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Original article

Synthesis and pharmacological activity of *O*-aminoalkyl derivatives of 7-hydroxycoumarin

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ABSTRACT

A series of novel *O*-aminoalkyl substituted 7-hydroxycoumarins were synthesized and evaluated for antibacterial and anticancer toxicity. Two different synthetic procedures, conventional and microwave assisted were used, and the structures of the compounds were confirmed by IR, ^{1}H, ^{13}C NMR and MAS spectroscopic data. The molecular and crystal structures of 8-acetyl-7-[2-(1-morpholino)ethoxy] 4-methylchromen-2-one in solid state were analyzed by single crystal X-ray diffraction. The compound crystallizes in the monoclinic space group $P2_1/c$. The main driving forces for the supramolecular structure are the C–H···O hydrogen bonds and the π···π intermolecular interactions. The most active compounds are those, where the *O*-aminoalkyl substituent has *N*,*N*-diethylamino part, and acetyl group is at C6 or at C8 atoms.

1. Introduction

Coumarin and chromone derivatives are of great interest due to their diverse bioactivity [1]. In particular, their antibacterial, antifungal and anticancer activities make the compounds attractive for further derivatization and screening as novel therapeutic agents [2]. The literature investigation revealed cytotoxic activity of coumarins against several human tumor cell lines [3]. Auraptene: 7-[(*E*)-3,7-dimethylocta-2,6-dienyloxy]-2*H*-chromen-2-one, is a bioactive coumarin ether, isolated from members of the genus Citrus. Many studies have reported the effect of auraptene as a chemopreventative agent against cancers of skin, oral cavity, esophagus, and large bowel in rodent models. Geiparvarin: 7-{[(2*E*)-3-(5,5-dimethyl-4-oxo-4,5-dihydrofuran-2-yl)but-2-en-1-yl]oxy}-2*H*-chromen-2-one, a naturally occurring coumarin compound shows significant inhibitory activity against several cell lines including sarcoma 180, Lewis lung carcinoma P-388, lymphocytic leukemia. Moreover, the use of aminoalkyl ethers of phenols as anticancer agents for the breast and colon human cancer cell lines has been described [4].

The antibacterial activity of coumarin *per se* and substituted coumarins was evaluated and their structure against activity was analyzed. It was shown [5] that coumarins with a methoxy function at C-7 are effective against Gram-negative bacteria and the Gram-positive strains of *Staphylococcus aureus.* On the other hand, coumarins having at least two methoxy and at least one additional phenolic groups emerge as promising candidates with broad-spectrum antibacterial activity. Moreover, the antifungal potential of osthenol: 7-hydroxy-8-(3-methylbut-2-enyl)chromen-2-one, can be related to the presence of the branched alkyl group at C-8 position [6].

Based on this these findings and as a continuation of our previous research [7–9], we have planned synthesis and the evaluation of biological activity of coumarin derivatives bearing *O*-aminoalkyl, methyl and acetyl substituents at positions 4, 6, 7 and 8 (see Scheme 1). In the present paper we report their synthesis under conventional conditions and discuss advantages of using microwave-assisted method as well as their anticancer and antimicrobial activity. Additionally, the X-ray structure of 8-acetyl-7-[2-(1-morpholino)ethoxy]4-methylchromen-2-one (**5d**) is presented together with the inter and intramolecular interactions in solid state.

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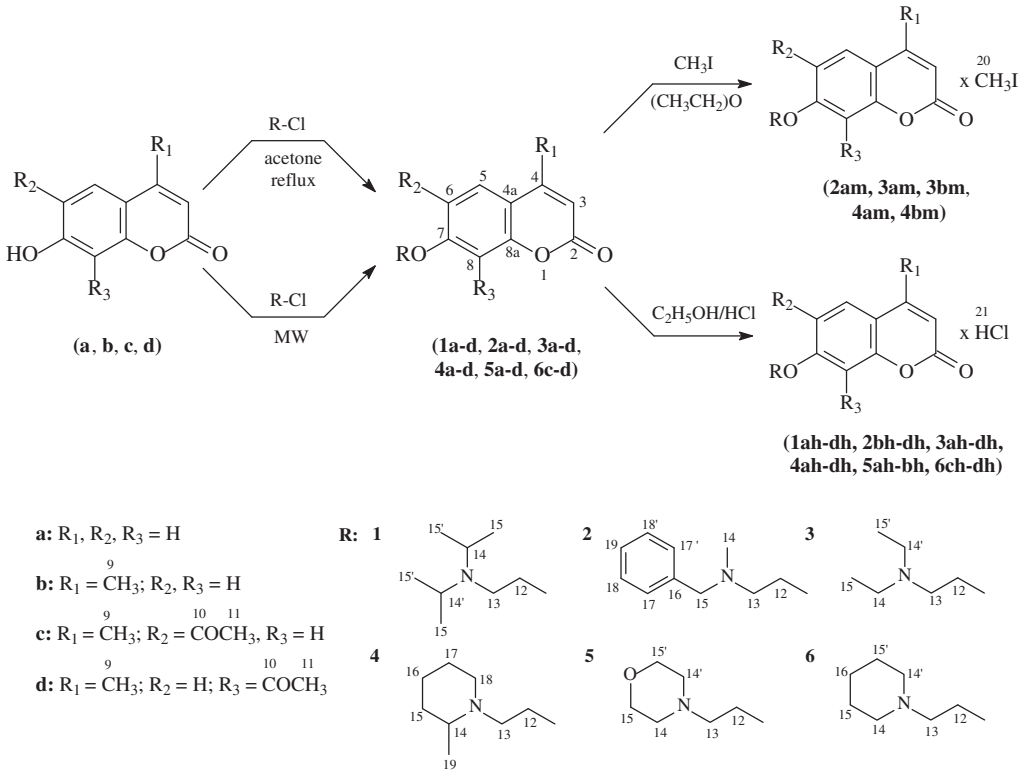

Scheme 1. Syntheses of *O*-aminoalkyl derivatives of 7-hydroxycoumarin.

2. Results and discussion

2.1. Chemistry

The planned compounds were obtained from 7-hydroxy and 4-, 6- or 8-substituted coumarin. In the first step the corresponding *O*-alkylamino derivatives **1a–d**, **2a–d**, **3a–d**, **4a–d**, **5a–d** and **6c–d** were prepared by alkylation of the phenolic group with appropriate chloroethylamines (Scheme 1). Two methods were employed, conventional and with microwave irradiation (see Supplementary data). Microwave irradiation was used in order to shorten time of reaction as well as increase yield, and sometimes it was the only method that could be used [9]. In the second step, the majority of *O*-alkylamino derivatives were converted into the hydrochlorides **1ah–dh**, **2bh–dh**, **3ah–dh**, **4ah–dh**, **5ah–bh**, **6ch–dh** or the methiodides **2am**, **3am**, **3bm**, **4am**, **4bm** to increase solubility in polar solvents.

2.2. Crystal structure of 8-acetyl-7-[2-(1-morpholino)ethoxy]4-methylchromen-2-one (*5d*)

The molecular and crystal structures of 8-acetyl-7-[2-(1-morpholino)ethoxy]4-methylchromen-2-one (**5d**) in solid state were analyzed by single crystal X-ray diffraction. A view of the molecular structure together with the atomic numbering scheme is shown in Fig. 1 (the drawings were performed with Mercury program [10]). The results indicate that the compound **5d** crystallizes in the monoclinic space group $P2_1/c$ with one ordered molecule in the asymmetric unit. The bond lengths and angles in the coumarin ring system compare well with those observed in other coumarin derivatives [7,8,11–15]. The coumarin moiety is almost planar with a maximum deviation of 0.046(1) Å for O2. The dihedral angle between the least-squares planes of the pyrone and benzene rings is 1.97(4)°. The C9 and O7 atoms are nearly coplanar with the coumarin ring system. The acetyl group at C8 is considerably twisted with respect to the plane of the coumarin fragment as indicate the C7–C8–C10–C11 and C7–C8–C10–O11 torsion angles (the values of the appropriate torsion angles are given in Table S2 in Supplementary data). In consequence the C11 and O11 atoms are found above and below of the best plane of the coumarin moiety. This orientation is quite different compared with 8-acetyl-7-hydroxy-4-methylcoumarin [7]. The orientation of the substituent at C7 with respect to the two-ring framework can be described by the torsion angle C8–C7–O7–C12 of −174.7(1)°. The chain between C7 and N13 atoms is in an extended *trans* conformation and the morpholine ring adopts the conformation of a chair. The best plane of the coumarin fragment and the C14/C15/C14′/C15′ plane make an angle of 44.29(6)°.

In the crystal of **5d**, the packing of molecules is stabilized by intermolecular C–H···O hydrogen bonds and stacking forces. The geometric parameters of all intermolecular interactions are given in Table 1. The molecules are linked by C6–H6A···O15(x, $1.5-y$, $0.5+z$), C12–H12B···O15 (x, $1.5-y$, $0.5+z$) and C11–H11A···O2

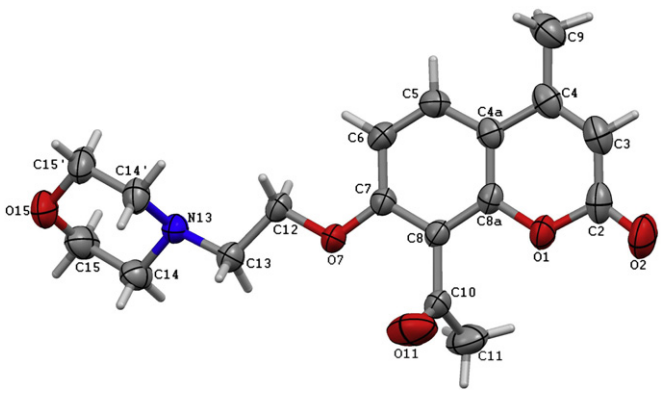

Fig. 1. A view of the molecule of **5d**.

Table 1
Hydrogen bonding geometry [Å and °] for **5d**.

D–H···A	d (D–H)	d(H···A)	d(D···A)	<(DHA)
C9–H9B···O11[i]	0.96	2.71	3.600(2)	154
C6–H6A···O15[ii]	0.93	2.54	3.463(2)	175
C12–H12B···O15[ii]	0.97	2.67	3.289(2)	122
C11–H11A···O2[iii]	0.96	2.72	3.402(2)	128
C14′–H14D···O2[iv]	0.97	2.79	3.589(2)	140
C15′–H15C···O1[iv]	0.97	2.78	3.595(2)	142
C15–H15B···O2[v]	0.97	2.80	3.465(2)	126

Symmetry codes: (i) $-x$, $1-y$, $1-z$; (ii) x, $1.5-y$, $0.5+z$; (iii) x, $0.5-y$, $-0.5+z$;(iv) $-x$, $0.5+y$, $0.5-z$; (v) $1-x$, $0.5+y$, $0.5-z$.

(x, $0.5-y$, $-0.5+z$) hydrogen bonds forming layers parallel to the (100) plane (Fig. 2). C9–H9B···O11 ($-x$, $1-y$, $1-z$), C14′–H14D···O2 ($-x$, $0.5+y$, $0.5-z$), C15′–H15C···O1 ($-x$, $0.5+y$, $0.5-z$) contacts and π···π stacking forces connect adjacent layers into bilayers. In the stacks, cohesion between molecules results in π···π interactions by partly overlapping coumarin units from neighboring layers (details are given in Supplementary data).

2.3. Pharmacological screening

2.3.1. Anticancer screening

Three compounds, 7-[2-(*N*,*N*-diisopropylamino)ethoxy] 4-methylchromen-2-one (**1b**), 8-acetyl-7-[2-(2-methylpiperidinyl) ethoxy]4-methylchromen-2-one (**4d**) and 6-acetyl-7-[2-(1-morpholino)ethoxy]4-methylchromen-2-one (**5c**) were selected by the Division of Cancer Treatment and Diagnosis, National Cancer Institute Bethesda, USA to be evaluated in the full panel of 60 different cell lines, representing human leukemia, non-small cell lung cancer, colon cancer, central nervous system (CNS) cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer cell lines (the details are available at the web site http://dtp.nci.nih.gov).

The growth inhibition (GI) was measured at the concentration of 10^{-5} M, which is further explained at the web site http://dtp.nci.nih.gov/branches/btb/onedose_interp.html.

Compound **1b** was found to be inactive. Compound **4d** inhibited the growth of renal cancer 786-0, GI = 45.94, and slightly inhibited the growth of leukemia cell line HL-60 (TB), GI = 31.95. Compound **5c** appears to be somewhat more active. It inhibited the growth of leukemia CCRF-CEM (GI = 62.71), non-small cell lung cancer HOP-92 (GI = 23.78) and colon cancer HCC-2998 (GI = 34.14).

2.3.2. Antimicrobial screening

The majority of 7-hydroxycoumarin derivatives were evaluated as salts with the exception of compounds **2c**–**d** and **5a**–**d** which were soluble in polar solvent enough to perform the measurements. The activity of novel derivatives was compared with the activity of 7-hydroxycoumarin (**a**), 7-hydroxy-4-methylcoumarin (**b**), 6-acetyl-7-hydroxy-4-coumarin (**c**) and 8-acetyl-7-hydroxy-4-coumarin (**d**), which were used as the model compounds. Compound **a** was not active against all tested strains, while compound **b** was slightly active against *Bacillus cereus*. Compounds **c** and **d** showed some activity against *Bacillus* strains, and lower

Table 2
Antibacterial activity of synthesized novel series of 7-hydroxycoumarins.

Compound	MIC μmol/mL							
	M.l.[a]	M.l.[b]	B.s.[c]	B.c.[d]	S.a.[e]	S.a.[f]	E.c.[g]	E.c.[h]
a	–[i]	–[i]	–[i]	–[i]	–[i]	–[i]	–[i]	–[i]
b	–[i]	–[i]	–[i]	85.1	–[i]	–[i]	–[i]	–[i]
c	45.8	45.8	22.9	4.6	45.8	–[i]	–[i]	–[i]
d	68.7	68.7	45.8	22.9	68.7	–[i]	–[i]	–[i]
1ah	46.0	61.4	46.0	30.7	–[i]	61.4	61.4	46.0
1bh	7.4	44.1	2.9	2.9	44.1	44.1	44.1	14.7
1ch	37.5	37.5	12.5	12.5	–[i]	–[i]	–[i]	–[i]
1dh	25.0	–[i]	–[i]	–[i]	–[i]	–[i]	–[i]	–[i]
2bh	40.7	40.7	–[i]	–[i]	–[i]	–[i]	–[i]	–[i]
2ch	1.5	1.5	24.3	24.3	24.3	24.3	24.3	24.3
2dh	6.0	6.0	2.4	2.4	35.7	23.8	–[i]	35.7
3ah	8.4	16.8	8.4	8.4	–[i]	67.2	33.6	16.8
3bh	2.0	8.0	2.0	2.0	32.1	32.1	8.0	8.0
3c	31.5	31.5	31.5	63.0	–[i]	–[i]	–[i]	–[i]
3ch	1.8	1.8	0.4	0.4	7.1	7.1	14.1	7.1
3d	2.0	2.0	3.9	3.9	3.9	3.9	–[i]	–[i]
3dh	3.5	14.1	–[i]	–[i]	–[i]	–[i]	–[i]	–[i]
4ah	15.4	30.9	30.9	30.9	46.3	61.8	15.4	30.9
4bh	14.4	14.4	14.4	28.8	43.2	28.8	7.2	14.4
4ch	6.6	13.2	1.6	1.6	26.3	26.3	–[i]	26.3
4dh	12.3	24.6	24.6	24.6	24.6	24.6	36.9	49.2
6ch	1.7	1.7	1.7	1.7	13.3	6.7	26.7	13.3
6dh	6.5	13.0	39.1	26.1	39.1	39.1	26.1	13.0
5a	18.2	18.2	72.6	72.6	72.6	36.3	36.3	36.3
5b	8.6	8.6	69.1	69.1	–i	69.1	51.8	51.8
5c	30.2	30.2	30.2	30.2	30.2	30.2	30.2	30.2
5d	30.2	30.2	–[i]	–[i]	–[i]	–[i]	–[i]	–[i]
2am	1.4	5.5	21.9	21.2	21.2	21.2	21.2	21.2
4bm	22.6	22.6	22.6	45.1	–[i]	–[i]	–[i]	–[i]

[a] M.l.: *Micrococcus luteus* ATCC 9341 (Gram-positive bacterial strain).
[b] M.l.: *Micrococcus luteus* ATCC 10240 (Gram-positive bacterial strain).
[c] B.s.: *Bacillus subtilis* ATCC 6633 (Gram-positive bacterial strain).
[d] B.c.: *Bacillus cereus* ATCC 11778 (Gram-positive bacterial strain).
[e] S.a.: *Staphylococcus aureus* ATCC 6538 (Gram-positive bacterial strain).
[f] S.a: *Staphylococcus aureus* ATCC 6538P (Gram-positive bacterial strain).
[g] E.c.: *Escherichia coli* ATCC 8739 (Gram-negative bacterial strain).
[h] E.c.: *Escherichia coli* ATCC 10536 (Gram-negative bacterial strain).
[i] Not active in the concentration 20 mg/mL.

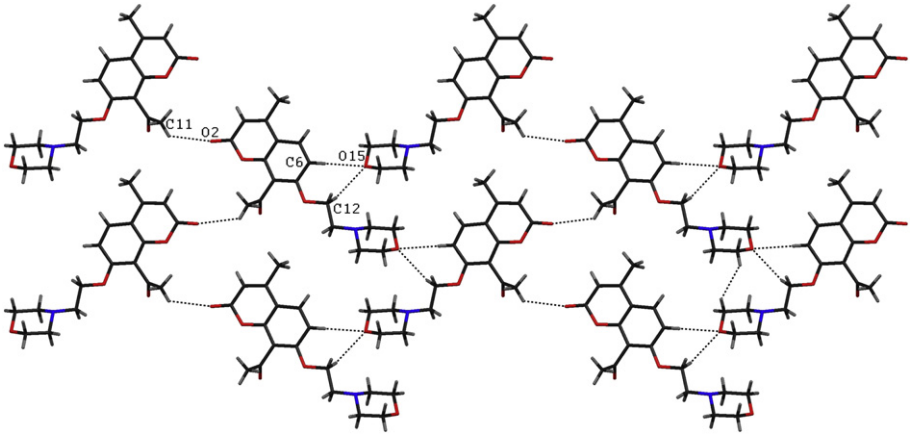

Fig. 2. The interconnections within a layer.

activity against *Micrococcus* and *Staphylococcus* strains. The compounds that are more active in antimicrobial screening than the model compounds are shown in Table 2.

The most active derivatives are **3ch** and **3d**, in which the *O*-aminoalkyl substituent has *N*,*N*-diethylamino part, and acetyl group is present at C6 (in **3ch**) or at C8 (in **3d**) atoms. Compound **3ch** does not only inhibit growth of *Bacillus subtilis* and *B. cereus* strains in the lowest concentration (MIC = 0.4–1.8 μmol/mL), but is also active against all bacterial strains used in the test. Compounds **3ah** and **3bh** are also active, but because they lack the acetyl group, their activity against *Staphylococcus* is decreased. Compounds **2ch** and **2dh** with benzyl and **6ch** with piperidine groups, and also with acetyl group showed some activity against *Micrococcus luteus* and *Bacillus* strains. All five methyliodies, **2am**, **3am**, **3bm**, **4am** and **4bm** were tested, but only **2am** bearing benzyl ring was active against *M. luteus*.

Antimicrobial activity of the tested compounds against Gram-negative and Gram-positive bacterial strains suggests that other effects than those related only to the composition of bacterial wall may be implicated in bacteria growth inhibition. The mechanism of their action is probably related in different enzymatic routes in particular bacterial strains.

3. Conclusion

The presented synthetic procedures allowed to obtain 7-hydroxycoumarin derivatives with good yields. Application of microwave irradiation considerably increased rate and yield of the reactions as well as the purity of the products. 8-Acetyl-7-[2-(1-morpholino)ethoxy]4-methylchromen-2-one crystallizes in the monoclinic space group $P2_1/c$. The molecules are linked by C–H···O contacts type of the hydrogen bonds, length of 2.54–2.80 Å. Three-dimensional supramolecular structure results from combination of intermolecular C–H···O hydrogen bonds and π···π stacking forces.

Alkylamination of OH group at C7 atom of coumarin resulted in compounds with better antibacterial activity than the model molecules. The compounds found to be most active are those, in which the *O*-aminoalkyl substituent has *N*,*N*-diethylamino part, and acetyl group was present at C6 or at C8 atoms. 6-Acetyl-7-[2-(1-morpholino)ethoxy]4-methylchromen-2-one inhibited the growth of leukemia CCRF-CEM (GI = 62.71) at the concentration of 10^{-5} M.

4. Experimental protocols

4.1. General methods

Melting points were determined with ElectroThermal 9001 Digital Melting Point apparatus and are uncorrected. Microwave oven Plazmatronika 1000 W equipped with a single mode cavity suitable for the microscale synthesis and microwave choked outlet connected to external condenser set to 30% power, was used (http://www.plazmatronika.com.pl). Microanalysis was carried in the Department of Analytical Chemistry, Warsaw Technical University using Vario EL III, Elementar GmbH. High resolution mass spectra were recorded on Quattro LCT (TOF). ^{1}H NMR, ^{13}C NMR, HSQC and HMBC spectra in solution were recorded at 25 °C with a Varian NMRS-300 or Varian Unity plus-500 spectrometers (as indicated in the text) and standard Varian software was employed. The calculated shielding constants were used as an aid in an assignment of resonances of ^{13}C atoms. Chemical shifts δ [ppm] were referenced to TMS. The notation used in detailed description of NMR resonances is given in Scheme 1. IR spectra were recorded on an FT IR Perkin–Elmer instrument. TLC was carried out using Kieselgel 60 F_{254} sheets and spots were visualized by UV – 254 and 365 nm.

4.2. General procedures for O-alkylation compounds **a**, **b**, **c** and **d**

4.2.1. Conventional syntheses to obtain compounds **1a–d**, **2a–d**, **3a–d**, **4a–d**, **5a–d**, **6c–d**

7-Hydroxycoumarin (**a**) or 7-hydroxy-4-methylcoumarin (**b**), 6-acetyl-7-hydroxy-4-methylcoumarin (**c**), 8-acetyl-7-hydroxy-4-methylcoumarin (**d**) (3 mmol) and appropriate alkylating agent $R_{1-6}Cl$ (3.3–4.5 mmol) dissolved in dry acetone as well as anhydrous potassium carbonate (15.6 mmol) were added into the flask. The mixture was refluxed and monitored by TLC on silica gel plates, (eluents and R_f values are shown together with structural data). After completion of each reaction as indicated by TLC, the inorganic salts were filtered out and the volume of the mixture was reduced by half due to evaporation. The final solution was poured out to the flask with water and ice, stirred for 30 min and then the mixtures were treated according to the method described as follows.

Procedure I: the precipitate was filtered out, washed with water, dried and crystallized.

Procedure II: the mixture was extracted with chloroform. The organic layer was dried over anh. Na_2SO_4. The solvent was evaporated and the solid residue was crystallized.

The yields of products and synthetic details are also presented in Table S1 in Supplementary data.

4.2.2. Microwave-assisted syntheses to obtain compounds **1a–d**, **2a–d**, **3a–d**, **4a–b**, **4d**, **5a–b**, **5d**, **6c–d**

7-Hydroxycoumarin (**a**) or 7-hydroxy-4-methylcoumarin (**b**), 6-acetyl-7-hydroxy-4-methylcoumarin (**c**), 8-acetyl-7-hydroxy-4-methylcoumarin (**d**) (1 mmol) and appropriate alkylating agent $R_{1-6}Cl$ (1.1–1.5 mmol), dry acetone (5 mL) or 1-methyl-2-pyrrolidone (0.5–2 mL) as well as anhydrous potassium carbonate (5.2 mmol) were added into the flask. The mixture was heated under reflux in the monomode microwave oven under the conditions described in Table 1 (see Supplementary data). The reaction was monitored by TLC in the same way as described in the traditional method. Procedures I and II (see the general procedure in Section 4.2.1) were used to isolate products. Some compounds were pure enough for the structural characterization. The yields of products and synthetic details are also presented in Table S1 in Supplementary data.

Syntheses and analytical data of compounds **1a** and **1b** have been described in our previous work [8].

4.2.3. 6-Acetyl-7-[2-(N,N-diisopropylamino)ethoxy]4-methylchromen-2-one (**1c**)

M.p.: 117–117.5 °C (cyclohexane); eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt 10:3:1), R_f (**1c**) = 0.22; IR (KBr) cm^{-1}: 3074 ($\nu_{C-Harom}$), 2962 ($\nu_{C-Hasym}$), 2863 (ν_{C-Hsym}), 1735, 1677 ($\nu_{C=O}$), 1621, 1604, 1496 ($\nu_{C=C}$), 1465 ($\delta_{C-Hasym}$), 1388 (δ_{C-Hsym}), 1283 ($\nu_{C-O-Casym}$), 1056 ($\nu_{C-O-Csym}$), 849 (γ_{C-H}); ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ ppm: 1.06 (d, J = 6.5 Hz, 12H, H-15, 15′), 2.45 (d, J = 1.5 Hz, 3H, H-9), 2.63 (s, 3H, H-11), 3.03 (t, J = 6.8 Hz, 2H, H-13), 3.14 (heptet, J = 6.5 Hz, 2H, H-14, 14′), 4.22 (t, J = 6.8 Hz, 2H, H-12), 6.17 (bq, J = 1.5 Hz, 1H, H-3), 7.02 (s, 1H, H-8), 7.97 (s, 1H, H-5); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ ppm: 18.43 (C-9), 21.26 (C-15, 15′), 32.23 (C-11), 44.45 (C-13), 49.59 (C-14, 14′), 70.94 (C-12), 101.63 (C-8), 113.16 (C-3), 113.90 (C-4a), 125.94 (C-6), 128.20 (C-5), 153.68 (C-4), 158.38 (C-8a), 160.23 (C-7), 162.02 (C-2), 197.41 (C-10). TOF MS ES+: $[M+H]^+$ calcd for $C_{20}H_{28}NO_4$: 346.2018 found 346.1993.

4.2.4. 8-Acetyl-7-[2-(N,N-diisopropylamino)ethoxy]4-methylchromen-2-one (**1d**)

M.p.: 96.5–97 °C (cyclohexane); eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt 10:3:1), R_f (**1d**) = 0.27.;IR (KBr)cm^{-1}:

3074 ($\nu_{C-Harom}$), 2959 ($\nu_{C-Hasym}$), 2867 (ν_{C-Hsym}), 1726, 1713 ($\nu_{C=O}$), 1604, 1566, 1496, 1450 ($\nu_{C=C}$), 1462 ($\delta_{C-Hasym}$), 1385 (δ_{C-Hsym}), 1296 ($\nu_{C-O-Casym}$), 1080 ($\nu_{C-O-Csym}$), 847 (γ_{C-H}); ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ ppm: 1.03 (d, $J = 6.5$ Hz, 12H, H-15, 15′), 2.45 (d, $J = 1.0$ Hz, 3H, H-9), 2.53 (s, 3H, H-11), 2.88 (t, $J = 6.5$ Hz, 2H, H-13), 3.09 (heptet, $J = 6.5$ Hz, 2H, H-14, 14′), 4.11 (t, $J = 6.5$ Hz, 2H, H-12), 6.15 (bq, $J = 1.0$, 1H, H-3), 7.13 (d, $J = 8.8$ Hz, 1H, H-6), 7.77 (d, $J = 8.8$ Hz, 1H, H-5); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ ppm: 18.63 (C-9), 21.27 (C-15, 15′), 32.53 (C-11), 44.56 (C-13), 49.67 (C-14, 14′), 71.09 (C-12), 109.60 (C-6), 112.79 (C-3), 114.63 (C-4a), 120.37 (C-8), 127.64 (C-5), 151.33 (C-8a), 153.59 (C-4), 158.86 (C-7), 160.00 (C-2), 199.04 (C-10). TOF MS ES+: $[M + H]^+$ calcd for $C_{20}H_{28}NO_4$: 346.2018 found 346.2022.

4.2.5. 7-[2-(N-Benzyl-N-methylamino)ethoxy]chromen-2-one (**2a**)

Oil (column: $CHCl_3$–AcOEt; 9:1); eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt–MeOH 10:3:1:1), R_f (**2a**) = 0.68; IR (KBr) cm^{-1}: 3062 ($\nu_{C-Harom}$), 2962 ($\nu_{C-Hasym}$), 2863 (ν_{C-Hsym}), 1725 ($\nu_{C=O}$), 1614, 1505, 1491, 1449 ($\nu_{C=C}$), 1461 ($\delta_{C-Hasym}$), 1373 (δ_{C-Hsym}), 1261 ($\nu_{C-O-Casym}$), 1021 ($\nu_{C-O-Csym}$), 799 (γ_{C-H}); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.37 (s, 3H, H-14), 2.87 (t, $J = 5.7$ Hz, 2H, H-13), 3.64 (s, 2H, H-15), 4.16 (t, $J = 5.7$ Hz, 2H, H-12), 6.24 (d, $J = 9.6$ Hz, 1H, H-3), 6.80 (d, $J = 2.4$ Hz, 1H, H-8), 6.83 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.4$ Hz, 1H, H-6), 7.23–7.34 (m, 5H, H-17, 17′, 18, 18′, 19), 7.35 (d, $J = 8.4$ Hz, 1H, H-5), 7.62 (d, $J = 9.6$ Hz, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 43.17 (C-14), 55.55 (C-13), 62.90 (C-15), 67.09 (C-12), 101.70 (C-8), 112.77 (C-4a), 113.13 (C-6), 113.30 (C-3), 127.45 (C-19), 128.53 (C-17, 17′), 128.90 (C-5), 129.26 (C-18, 18′), 138.55 (C-16), 143.61 (C-4), 156.04 (C-8a), 161.37 (C-2), 162.21 (C-7). TOF MS ES+: $[M + H]^+$ calcd for $C_{19}H_{20}NO_3$: 310.1443 found 310.1411.

4.2.6. 7-[2-(N-Benzyl-N-methylamino)ethoxy]4-methylchromen-2-one (**2b**)

M.p.: 57–58 °C (petroleum ether); eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt 10:3:1:), R_f (**2b**) = 0.32; IR (KBr) cm^{-1}: 3061 ($\nu_{C-Harom}$), 2936 ($\nu_{C-Hasym}$), 2837 (ν_{C-Hsym}), 1711 ($\nu_{C=O}$), 1616, 1509, 1492 ($\nu_{C=C}$), 1451 ($\delta_{C-Hasym}$), 1392 (δ_{C-Hsym}), 1280 ($\nu_{C-O-Casym}$), 1021 ($\nu_{C-O-Csym}$), 831 (γ_{C-H}); ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ ppm: 2.32 (s, 3H, H-14), 2.43 (s, 3H, H-9), 2.86 (t, $J = 6.0$ Hz, 2H, H-13), 3.63 (s, 2H, H-15), 4.26 (t, $J = 6.0$ Hz, 2H, H-12), 6.12 (s, 1H, H-3), 6.88 (d, $J = 2.1$ Hz, 1H, H-8), 6.94 (dd, $J_1 = 2.1$ Hz, $J_2 = 8.7$ Hz, 1H, H-6), 7.20–7.38 (m, 5H, H-17, 17′, 18, 18′, 19), 7.66 (d, $J = 8.7$ Hz, 1H, H-5); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ ppm: 18.61 (C-9), 43.17 (C-14), 56.46 (C-13), 63.22 (C-15), 68.05 (C-12), 102.19 (C-8), 112.46 (C-3), 113.33 (C-6), 114.40 (C-4a), 127.09 (C-5), 127.82 (C-19), 129.07 (C-17, 17′), 129.73 (C-18, 18′), 140.47 (C-16), 153.76 (C-4), 156.40 (C-8a), 160.97 (C-7), 163.09 (C-2). TOF MS ES+: $[M + H]^+$ calcd for $C_{20}H_{22}NO_3$: 324.1600 found 324.1588.

4.2.7. 6-Acetyl-7-[2-(N-benzyl-N-methylamino)ethoxy]4-methylchromen-2-one (**2c**)

M.p.: 126.5–127 °C (cyclohexane:acetone, 4:1); eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt–MeOH 10:3:1:1), R_f (**2c**) = 0.60; IR (KBr) cm^{-1}: 3075 ($\nu_{C-Harom}$), 2979, 2947 ($\nu_{C-Hasym}$), 2884, 2842 (ν_{C-Hsym}), 1728, 1670 ($\nu_{C=O}$), 1599, 1493, 141447 ($\nu_{C=C}$), 1459 ($\delta_{C-Hasym}$), 1385 (δ_{C-Hsym}), 1283 ($\nu_{C-O-Casym}$), 1055 ($\nu_{C-O-Csym}$), 731 (γ_{C-H}); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.36 (s, 3H, H-14), 2.43 (d, $J = 1.2$ Hz, 3H, H-9), 2.63 (s, 3H, H-11), 2.93 (t, $J = 5.4$ Hz, 2H, H-13), 3.62 (s, 2H, H-15), 4.23 (t, $J = 5.4$ Hz, 2H, H-12), 6.17 (bq, $J = 1.2$ Hz, 1H, H-3), 6.82 (s, 1H, H-8), 7.26–7.32 (m, 5 H, H-17, 17′ 18, 18′ 19), 8.05 (s, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 18.91 (C-9), 32.34 (C-11), 42.99 (C-14), 55.78 (C-13), 63.19 (C-15), 67.57 (C-12), 100.75 (C-8), 113.06 (C-3), 113.68 (C-4a), 125.22 (C-6), 127.58 (C-19), 128.16 (C-17, 17′), 128.63 (C-18, 18′), 129.22 (C-5), 139.47 (C-16), 152.97 (C-4), 157.75 (C-8a), 160.56 (C-7), 161.16 (C-2), 197.99 (C-10). TOF MS ES+: $[M + H]^+$ calcd for $C_{22}H_{24}NO_4$: 366.1705 found 366.1719.

4.2.8. 8-Acetyl-7-[2-(N-benzyl-N-methylamino)ethoxy]4-methylchromen-2-one (**2d**)

M.p.: 104–104.5 °C (cyclohexane); eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt 10:3:1:), R_f (**2d**) = 0.11; IR (KBr) cm^{-1}: 3065 ($\nu_{C-Harom}$), 2977, 2960 ($\nu_{C-Hasym}$), 2882, 2853 (ν_{C-Hsym}), 1741, 1704 ($\nu_{C=O}$), 1600, 1565, 1494, 1453 ($\nu_{C=C}$), 1460 ($\delta_{C-Hasym}$), 1383 (δ_{C-Hsym}), 1293 ($\nu_{C-O-Casym}$), 1094 ($\nu_{C-O-Csym}$), 873 (γ_{C-H}); ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ ppm: 2.29 (s, 3H, H-14), 2.45 (d, $J = 1.2$ Hz, 3H, H-9), 2.53 (s, 3H, H-11), 2.84 (t, $J = 5.7$ Hz, 2H, H-13), 3.60 (s, 2H, H-15), 4.32 (t, $J = 5.7$ Hz, 2H, H-12), 6.16 (bq, $J = 1.2$ Hz, 1H, H-3), 7.12 (d, $J = 15.0$ Hz, 1H, H-6), 7.20–7.38 (m, 5 H, H-17, 17′, 18, 18′, 19), 7.75 (d, $J = 15.0$ Hz, 1H, H-5); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ ppm: 18.71 (C-9), 32.55 (C-11), 42.95 (C-14), 56.49 (C-13), 63.25 (C-15), 68.48 (C-12), 109.61 (C-6), 112.94 (C-3), 114.82 (C-4a), 120.45 (C-8), 127.73 (C-19), 127.81 (C-5), 129.09 (C-17, 17′), 129.68 (C-18, 18′), 140.40 (C-16), 151.30 (C-8a), 153.67 (C-4), 158.77 (C-7), 160.07 (C-2), 199.17 (C-10). TOF MS ES+: $[M + H]^+$ calcd for $C_{22}H_{24}NO_4$: 366.1705 found 366.1715.

4.2.9. 7-[2-(N,N-Diethylamino)ethoxy]chromen-2-one (**3a**) [16,17]

M.p.: 47.7–48.2 °C (without crystallization after microwave-assisted synthesis) (lit. m.p.: 46 °C [16]); eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt–MeOH 10:3:1:1), R_f (**3a**) = 0.14; IR (KBr) cm^{-1}: 3082 ($\nu_{C-Harom}$), 2964 ($\nu_{C-Hasym}$), 2870 (ν_{C-Hsym}), 1724 ($\nu_{C=O}$), 1622, 1508, 1448 ($\nu_{C=C}$), 1469 ($\delta_{C-Hasym}$), 1388 (δ_{C-Hsym}), 1281 ($\nu_{C-O-Casym}$), 1025 ($\nu_{C-O-Csym}$), 832 (γ_{C-H}); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.09 (t, $J = 7.2$ Hz, 6H, H-15, 15′), 2.67 (q, $J = 7.2$ Hz, 4H, H-14, 14′), 2.92 (t, $J = 6.0$ Hz, 2H, H-13), 4.12 (t, $J = 6.0$ Hz, 2H, H-12), 6.24 (d, $J = 9.6$ Hz, 1H, H-3), 6.82 (d, $J = 2.4$ Hz, 1H, H-8), 6.85 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.4$ Hz, 1H, H-6), 7.36 (d, $J = 8.4$ Hz, 1H, H-5), 7.62 (d, $J = 9.6$ Hz, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 11.89 (C-15, 15′), 48.08 (C-14, 14′), 51.68 (C-13), 67.37 (C-12), 101.76 (C-8), 112.79 (C-4a), 113.13 (C-6), 113.33 (C-3), 128.99 (C-5), 143.58 (C-4), 156.07 (C-8a), 161.40 (C-2), 162.26 (C-7). TOF MS ES+: $[M + H]^+$ calcd for $C_{15}H_{20}NO_3$ 262.1443 found 262.1480.

4.2.10. 7-[2-(N,N-Diethylamino)ethoxy]4-methylchromen-2-one (**3b**)

M.p.: 50.1–50.7 °C (without crystallization after microwave-assisted synthesis); eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt–MeOH 10:3:1:1), R_f (**3b**) = 0.17; IR (KBr) cm^{-1}: 3077 ($\nu_{C-Harom}$), 2972 ($\nu_{C-Hasym}$), 2870 (ν_{C-Hsym}), 1717 ($\nu_{C=O}$), 1617, 1509 ($\nu_{C=C}$), 1472 ($\delta_{C-Hasym}$), 1392 (δ_{C-Hsym}), 1281 ($\nu_{C-O-Casym}$), 1021 ($\nu_{C-O-Csym}$), 842 (γ_{C-H}); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.11 (t, $J = 7.2$ Hz, 6H, H-15, 15′), 2.40 (d, $J = 1.0$ Hz, 3H, H-9), 2.70 (q, $J = 7.2$ Hz, 4H, H-14, 14′), 2.94 (t, $J = 6.0$ Hz, 2H, H-13), 4.14 (t, $J = 6.0$ Hz, 2H, H-12), 6.13 (bq, $J = 1.0$ Hz, 1H, H-3), 6.82 (d, $J = 2.4$ Hz, 1H, H-8), 6.87 (dd, $J_1 = 2.4$ Hz, $J_2 = 9.0$ Hz, 1H, H-6), 7.49 (d, $J = 9.0$ Hz, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 11.81 (C-15, 15′), 18.86 (C-9), 48.06 (C-14, 14′), 51.67 (C-13), 67.21 (C-12), 101.81 (C-8), 112.20 (C-3), 112.78 (C-6), 113.87 (C-4a), 125.71 (C-5), 152.71 (C-4), 155.45 (C-8a), 161.49 (C-2), 162.03 (C-7). TOF MS ES+: $[M + H]^+$ calcd for $C_{16}H_{22}NO_3$: 276.1600 found 276.1581.

4.2.11. 6-Acetyl-7-[2-(N,N-diethylamino)ethoxy]4-methylchromen-2-one (**3c**)

M.p.: 104.8–105.1 °C (cyclohexane); eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt–MeOH 10:3:1:1), R_f (**3c**) = 0.15; IR (KBr) cm^{-1}: 3077 ($\nu_{C-Harom}$), 2966 ($\nu_{C-Hasym}$), 2870 (ν_{C-Hsym}), 1733, 1712 ($\nu_{C=O}$), 1605, 1497 ($\nu_{C=C}$), 1471 ($\delta_{C-Hasym}$), 1388 (δ_{C-Hsym}), 1283 ($\nu_{C-O-Casym}$), 1058 ($\nu_{C-O-Csym}$), 836 (γ_{C-H}); ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ ppm: 1.03 (t, $J = 7.0$ Hz, 6H, H-15, 15′), 2.47 (d, $J = 1.5$ Hz,

3H, H-9), 2.63 (q, $J = 7.0$ Hz, 4H, H-14, 14′), 2.64 (s, 3H, H-11), 2.97 (t, $J = 6.0$ Hz, 2H, H-13), 4.34 (t, $J = 6.0$ Hz, 2H, H-12), 6.20 (bq, $J = 1.5$ Hz, 1H, H-3), 7.07 (s, 1H, H-8), 8.01 (s, 1H, H-5); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ ppm: 12.61 (C-15, 15′), 18.54 (C-9), 32.30 (C-11), 48.20 (C-14, 14′), 52.85 (C-13), 69.04 (C-12), 101.76 (C-8), 113.28 (C-3), 114.10 (C-4a), 126.15 (C-6), 128.35 (C-5), 153.87 (C-4), 158.53 (C-8a), 160.37 (C-7), 162.18 (C-2), 197.64 (C-10). TOF MS ES+: $[M + Na]^+$ calcd for $C_{18}H_{23}NO_4Na$: 340.1525 found 340.1489.

4.2.12. 8-acetyl-7-[2-(N,N-diethylamino)ethoxy]4-methylchromen-2-one (**3d**)

M.p.: 88.3–88.7 °C (cyclohexane); eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt–MeOH 10:3:1:1), R_f (**3d**) = 0.10; IR (KBr) cm^{-1}: 3092 ($\nu_{C-Harom}$), 2966 ($\nu_{C-Hasym}$), 2870 (ν_{C-Hsym}), 1725, 1708 ($\nu_{C=O}$), 1601, 1496 ($\nu_{C=C}$), 1439 broad ($\delta_{C-Hasym}$), 1384 (δ_{C-Hsym}), 1296 ($\nu_{C-O-Casym}$), 1074 ($\nu_{C-O-Csym}$), 811 (γ_{C-H}); ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ ppm: 1.00 (t, $J = 7.2$ Hz, 6H, H-15, 15′), 2.45 (d, $J = 1.5$ Hz, 3H, H-9), 2.54 (s, 3H, H-11), 2.58 (q, $J = 7.2$ Hz, 4H, H-14, 14′), 2.85 (t, $J = 6.0$ Hz, 2H, H-13), 4.23 (t, $J = 6.0$ Hz, 2H, H-12), 6.16 (bq, $J = 1.5$ Hz, 1H, H-3), 7.14 (d, $J = 9.0$ Hz, 1H, H-6), 7.77 (d, $J = 9.0$ Hz, 1H, H-5); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ ppm: 12.73 (C-15, 15′), 18.72 (C-9), 32.56 (C-11), 48.43 (C-14, 14′), 52.66 (C-13), 69.20 (C-12), 109.63 (C-6), 112.92 (C-3), 114.78 (C-4a), 120.52 (C-8), 127.74 (C-5), 151.41 (C-8a), 153.68 (C-4), 158.90 (C-7), 160.09 (C-2), 199.17 (C-10). TOF MS ES+: $[M + Na]^+$ calcd for $C_{18}H_{23}NO_4Na$: 340.1525 found 340.1510.

4.2.13. 7-[2-(2-Methylpiperidinyl)ethoxy]chromen-2-one (**4a**)

M.p.: 70–71 °C (cyclohexane); eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt–MeOH 10:3:1:1), R_f (**4a**) = 0.10; IR (KBr) cm^{-1}: 3085 ($\nu_{C-Harom}$), 2964, 2930 ($\nu_{C-Hasym}$), 2853, 2820 (ν_{C-Hsym}), 1724 ($\nu_{C=O}$), 1622, 1507, 1444 ($\nu_{C=C}$), 1474 ($\delta_{C-Hasym}$), 1376 (δ_{C-Hsym}), 1283 ($\nu_{C-O-Casym}$) 1022 ($\nu_{C-O-Csym}$), 830 (γ_{C-H}); ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ ppm: 1.08 (d, $J = 6.0$ Hz, 3H, H-19), 1.26 (m, 2H, Hax-15, 16), 1.51 (m, 2H, H-17), 1.58 (m, 2H, Heq-15, 16) 2.31 (dt, $J_1 = 11.5$ Hz, $J_2 = 4.0$ Hz, Hax-18), 2.39 (m, 1H, H-14), 2.72 (dt, $J_1 = 14.0$ Hz, $J_2 = 6.0$ Hz, Hax-13), 2.95 (dt, $J_1 = 11.5$ Hz, $J_2 = 4.0$ Hz, Heq-18), 3.09 (dt, $J_1 = 14.0$ Hz, $J_2 = 6.0$ Hz, Heq-13), 4.19 (t, $J = 6.0$ Hz, 2H, H-12), 6.21 (d, $J = 9.5$ Hz, 1H, H-3), 6.89 (d, $J = 2.4$ Hz, 1H, H-8), 6.92 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.5$ Hz, 1H, H-6), 7.56 (d, $J = 8.5$ Hz, 1H, H-5), 7.88 (d, $J = 9.5$ Hz, 1H, H-4); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ ppm: 19.64 (C-19), 24.65 (C-16), 27.06 (C-17), 35.55 (C-15), 53.34 (C-13), 53.97 (C-18), 56.90 (C-14), 67.96 (C-12), 102.10 (C-8), 113.44 (C-4a), 113.55 (C-6), 113.56 (C-3), 130.09 (C-5), 144.51 (C-4), 156.94 (C-8a), 160.93 (C-2), 163.23 (C-7). TOF MS ES+: $[M + H]^+$ calcd for $C_{17}H_{22}NO_3$: 288.1600 found 288.1559.

4.2.14. 7-[2-(2-Methylpiperidinyl)ethoxy]4-methylchromen-2-one (**4b**)

M.p.: 75–75.5 °C (cyclohexane); eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt–MeOH 10:3:1:1), R_f (**4b**) = 0.18; IR (KBr) cm^{-1}: 3079 ($\nu_{C-Harom}$), 2929 ($\nu_{C-Hasym}$), 2852 (ν_{C-Hsym}), 1711 ($\nu_{C=O}$), 1618, 1508, 1442 ($\nu_{C=C}$), 1461 ($\delta_{C-Hasym}$), 1392 (δ_{C-Hsym}), 1353, 1282 ($\nu_{C-O-Casym}$), 1072 ($\nu_{C-O-Csym}$), 843 (γ_{C-H}); ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ ppm: 1.10 (d, $J = 6.0$ Hz, 3H, H-19), 1.29 (m, 2H, Hax-15, 16), 1.55 (m, 2H, H-17), 1.63 (m, 2H, Heq-15, 16), 2.32 (dt broad, $J_1 = 11.0$ Hz, $J_2 = 3.5$ Hz, 1H, Hax-18), 2.40 (m, 1H, H-14), 2.45 (d, $J = 1.0$ Hz, 3H, H-9), 2.73 (dt, $J_1 = 14.0$ Hz, $J_2 = 6.0$ Hz, 1H, Hax-13), 2.94 (dt, $J_1 = 12.0$ Hz, $J_2 = 3.5$ Hz, 1H, Heq-18), 3.11 (dt, $J_1 = 14.0$ Hz, $J_2 = 6.0$ Hz, 1H, Heq-13), 4.21 (t, $J = 6.0$ Hz, 2H, H-12), 6.13 (bq, $J = 1.0$ Hz, 1H, H-3), 6.89 (d, $J = 2.5$ Hz, 1H, H-8), 6.95 (dd, $J_1 = 8.7$ Hz, $J_2 = 2.5$ Hz, 1H, H-6), 7.68 (d, $J = 8.7$ Hz, 1H, H-5); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ ppm: 18.61 (C-9), 19.76 (C-19), 24.76 (C-16), 27.15 (C-15), 35.64 (C-17), 53.42 (C-13), 54.07 (C-18), 57.00 (C-14), 67.96 (C-12), 102.15 (C-3), 112.40 (C-8), 113.31 (C-6), 114.31 (C-4a), 127.03 (C-5), 153.74 (C-4), 156.37 (C-8a), 160.95 (C-7), 163.15 (C-2). TOF MS ES+: $[M + H]^+$ calcd for $C_{18}H_{24}NO_3$: 302.1756 found 302.1719.

4.2.15. 6-Acetyl-7-[2-(2-methylpiperidinyl)ethoxy]4-methylchromen-2-one (**4c**)

M.p.: 113–113.2 °C (cyclohexane); eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt–MeOH 10:3:1:1), R_f (**4c**) = 0.29; IR (KBr) cm^{-1}: 3064 ($\nu_{C-Harom}$), 2925 ($\nu_{C-Hasym}$), 2830 (ν_{C-Hsym}), 1735 ($\nu_{C=O}$), 1605, 1555, 1496, 1449 ($\nu_{C=C}$), 1461 ($\delta_{C-Hasym}$), 1387 (δ_{C-Hsym}), 1280 ($\nu_{C-O-Casym}$), 1058 ($\nu_{C-O-Csym}$), 834 (γ_{C-H}); ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ ppm: 1.09 (d, $J = 6.0$ Hz, 3H, H-19), 1.20–1.38 (m, 2H, Hax-15, H-16), 1.44–1.67 (m, 4H, H-17, Heq-15, 16), 2.27 (td, $J_1 = 4.0$ Hz, $J_2 = 11.5$ Hz, 1H, Hax-18), 2.41 (m, 1H, H-14), 2.47 (d, $J = 1.2$ Hz, 3H, H-9), 2.65 (s, 3H, H-11), 2.71 (dt, $J_1 = 13.8$ Hz, $J_2 = 6.0$ Hz, 1H, Hax-13), 2.98 (dt, $J_1 = 4.0$ Hz, $J_2 = 11.5$ Hz, 1H, Heq-18), 3.25 (dt, $J_1 = 13.8$ Hz, $J_2 = 6.0$ Hz, 1H, Heq-13), 4.35 (m, 2H, H-12), 6.20 (bq, $J = 1.2$ Hz, 1H, H-3), 7.08 (s, 1H, H-8), 8.00 (s, 1H, H-5); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ ppm: 18.53 (C-9), 19.27 (C-19), 24.49 (C-16), 27.11 (C-17), 32.34 (C-11), 35.53 (C-15), 53.46 (C-13,18), 57.25 (C-14), 68.67 (C-12), 101.80 (C-8), 113.27 (C-3), 114.09 (C-4a), 126.15 (C-6), 128.32 (C-5), 153.86 (C-4), 158.53 (C-8a), 160.37 (C-2), 162.18 (C-7), 197.63 (C-10). TOF MS ES+: $[M + H]^+$ calcd for $C_{20}H_{26}NO_4$: 344.1862 found 344.1876.

4.2.16. 8-Acetyl-7-[2-(2-methylpiperidinyl)ethoxy]4-methylchromen-2-one (**4d**)

M.p.: 110–110.5 °C (petroleum ether); eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt–MeOH 10:3:1:1), R_f (**4d**) = 0.12; IR (KBr) cm^{-1}: 3084 ($\nu_{C-Harom}$), 2927 ($\nu_{C-Hasym}$), 2851 (ν_{C-Hsym}), 1706 ($\nu_{C=O}$), 1598, 1561, 1496 ($\nu_{C=C}$), 1455 ($\delta_{C-Hasym}$), 1373 (δ_{C-Hsym}), 1301 ($\nu_{C-O-Casym}$), 1076 ($\nu_{C-O-Csym}$), 837 (γ_{C-H}); ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ ppm: 1.06 (d, $J = 6.0$ Hz, 3H, H-19), 1.21–1.31 (m, 2H, Hax-15, 16), 1.46–1.55 (m, 2H, H-17), 1.56–1.65 (m, 2H, Heq-15, 16), 2.26 (td, $J_1 = 3.0$ Hz, $J_2 = 11.5$ Hz, 1H, Hax-18), 2.38 (m, 1H, H-14), 2.45 (d, $J = 1.5$ Hz, 3H, H-9), 2.55 (s, 3H, H-11), 2.70 (dt, $J_1 = 14.5$ Hz, $J_2 = 6.0$ Hz, 1H, Hax-13), 2.92 (dt, $J_1 = 11.5$ Hz, $J_2 = 3.0$ Hz, 1H, Heq-18), 3.10 (dt, $J_1 = 14.5$ Hz, $J_2 = 6.0$ Hz, 1H, Heq-13), 4.24 (t, $J = 6.0$ Hz, 2H, H-12), 6.15 (bq, $J = 1.5$ Hz, 1H, H-3), 7.14 (d, $J = 9.0$ Hz, 1H, H-6), 7.77 (d, $J = 9.0$ Hz, 1H, H-5); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ ppm: 18.63 (C-9), 19.50 (C-19), 24.54 (C-16), 27.00 (C-17), 32.52 (C-11), 35.49 (C-15), 53.26 (C-13), 53.77 (C-18), 56.96 (C-14), 68.54 (C-12), 109.57 (C-6), 112.81 (C-3), 114.67 (C-4a), 120.40 (C-8), 127.64 (C-5), 151.29 (C-8a), 153.59 (C-4), 158.79 (C-7), 159.99 (C-2), 199.09 (C-10). TOF MS ES+: $[M + H]^+$ calcd for $C_{20}H_{26}NO_4$: 344.1862 found 344.1858.

4.2.17. 7-[2-(1-Morpholino)ethoxy]chromen-2-one (**5a**)

M.p.: 87–87.5 °C (cyclohexane:acetone, 5:1); eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt–MeOH 10:3:1:1), R_f (**5a**) = 0.27; IR (KBr) cm^{-1}: 3077 ($\nu_{C-Harom}$), 2955, 2932 ($\nu_{C-Hasym}$), 2856, 2823 (ν_{C-Hsym}), 1725, 1705 ($\nu_{C=O}$), 1615, 1555, 1508, ($\nu_{C=C}$), 1462 ($\delta_{C-Hasym}$), 1372 (δ_{C-Hsym}), 1283 ($\nu_{C-O-Casym}$), 1043 ($\nu_{C-O-Csym}$), 837 (γ_{C-H}); ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ ppm: 2.54 (t, $J = 4.6$ Hz, 4H, H-14, 14′), 2.79 (t, $J = 5.8$ Hz, 2H, H-13), 3.62 (bt, $J = 4.6$ Hz, 4H, H-15, 15′), 4.26 (t, $J = 5.8$ Hz, 2H, H-12), 6.21 (d, $J = 9.5$ Hz, 1H, H-3), 6.90 (d, $J = 2.4$ Hz, 1H, H-8), 6.93 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.6$ Hz, 1H, H-6), 7.57 (d, $J = 8.6$ Hz, 1H, H-5), 7.88 (d, $J = 9.5$ Hz, 1H, H-4); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ ppm: 54.93 (C-14, 14′), 58.08 (C-13), 67.47 (C-15, 15′), 67.51 (C-12), 102.09 (C-8), 113.52 (C-4a), 113.55 (C-6), 113.65 (C-3), 130.12 (C-5), 144.51 (C-4), 156.91 (C-8a), 160.91 (C-7), 163.07 (C-2). TOF MS ES+: $[M + H]^+$ calcd for $C_{15}H_{18}NO_4$: 276.1236 found 276.1249.

*4.2.18. 7-[2-(1-Morpholino)ethoxy]4-methylchromen-2-one (**5b**)*

M.p.: 100-101 °C (hexane) (Lit. m.p: 102 °C (ethyl acetate) [18]); eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt–MeOH 10:3:1:1), R_f (**5b**) = 0.27; IR (KBr) cm^{-1}: 3075 ($\nu_{C-Harom}$), 2920, 2956 ($\nu_{C-Hasym}$), 2891, 2859 (ν_{C-Hsym}), 1726 broad ($\nu_{C=O}$), 1610, 1514 ($\nu_{C=C}$), 1476 ($\delta_{C-Hasym}$), 1392 (δ_{C-Hsym}), 1267 ($\nu_{C-O-Casym}$), 1071 ($\nu_{C-O-Csym}$), 871 (γ_{C-H}); ^1H NMR (300 MHz, $(CD_3)_2CO$) δ ppm: 2.43 (d, J = 1.2 Hz, 3H, H-9), 2.54 (bt, J = 4.8 Hz, 4H, H-14, 14′), 2.79 (t, J = 5.7 Hz, 2H, H-13), 3.61 (t, J = 4.8 Hz, 4H, H-15, 15′), 4.25 (t, J = 5.7 Hz, 2H, H-12), 6.11 (q, J = 1.2 Hz, 1H, H-3), 6.88 (d, J = 2.7 Hz, 1H, H-8), 6.94 (dd, J_1 = 9.0 Hz, J_2 = 2.7 Hz, 1H, H-6), 7.66 (d, J = 9.0 Hz, 1H, H-5); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ ppm: 18.61 (C-9), 55.03 (C-14, 14′), 58.18 (C-13), 67.56 (C-12, 15, 15′), 102.17 (C-8), 112.48 (C-3), 113.31 (C-6), 114.42 (C-4a), 127.08 (C-5), 153.74 (C-4), 156.36 (C-8a), 160.94 (C-7), 163.01 (C-2). TOF MS ES+: $[M + Na]^+$ calcd for $C_{16}H_{19}NO_4Na$: 312.1212 found 312.1227.

*4.2.19. 6-Acetyl-7-[2-(1-morpholino)ethoxy]4-methylchromen-2-one (**5c**)*

M.p.: 175.5–176.5 °C; eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt–MeOH 10:3:1:1), R_f (**5c**) = 0.38; IR (KBr) cm^{-1}: 3072 ($\nu_{C-Harom}$), 2952 ($\nu_{C-Hasym}$), 2859 (ν_{C-Hsym}), 1737, 1672 ($\nu_{C=O}$), 1604, 1499 ($\nu_{C=C}$), 1470 ($\delta_{C-Hasym}$), 1381 (δ_{C-Hsym}), 1284 ($\nu_{C-O-Casym}$), 1057 ($\nu_{C-O-Csym}$), 847 (γ_{C-H}); ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 2.47 (s, 3H, H-9), 2.55 (broad t, J = 4.4 Hz, 4H, H-14, 14′), 2.66 (s, 3H, H-11), 2.90 (t, J = 5.5 Hz, 2H, H-13), 3.62 (broad t, J = 4.4 Hz, 4H, H-15, 15′), 4.41 (t, J = 5.5 Hz, 2H, H-12), 6.20 (broad s, 1H, H-3), 7.07 (s, 1H, H-8), 8.01 (s, 1H, H-5); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ ppm: 18.53 (C-9), 32.30 (C-11), 54.77 (C-14, 14′), 58.00 (C-13), 67.61 (C-15, 15′), 67.76 (C-12), 101.75 (C-8), 113.31 (C-3), 114.17 (C-4a), 126.15 (C-6), 128.37 (C-5), 153.87 (C-4), 158.52 (C-8a), 160.39 (C-2), 162.07 (C-7), 197.62 (C-10). TOF MS ES+: $[M + Na]^+$ calcd for $C_{18}H_{21}NO_5Na$: 354.1317 found 354.1282.

*4.2.20. 8-Acetyl-7-[2-(1-morpholino)ethoxy]4-methylchromen-2-one (**5d**)*

M.p.: 100.5–101 °C (diethyl ether); eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt–MeOH 10:3:1:1), R_f (**5d**) = 0.20; IR (KBr) cm^{-1}: 3086 ($\nu_{C-Harom}$), 2977, 2917 ($\nu_{C-Hasym}$), 2865, 2826 (ν_{C-Hsym}), 1741, 1708 ($\nu_{C=O}$), 1602, 1567, 1499, 1454 ($\nu_{C=C}$), 1469 ($\delta_{C-Hasym}$), 1382 (δ_{C-Hsym}), 1293 ($\nu_{C-O-Casym}$), 1095 ($\nu_{C-O-Csym}$), 858 (γ_{C-H}); ^1H NMR (300 MHz, $(CD_3)_2CO$) δ ppm: 2.45 (d, J = 1.5 Hz, 3H, H-9), 2.51 (m, 4H, H-14, 14′), 2.55 (s, 3H, H-11), 2.77 (t, J = 5.4 Hz, 2H, H-13), 3.60 (bt, J = 4.5 Hz, 4H, H-15, 15′), 4.32 (t, J = 5.4 Hz, 2H, H-12), 6.16 (bq, J = 1.5 Hz, 1H, H-3), 7.15 (d, J = 9.0 Hz, 1H, H-6), 7.77 (d, J = 9.0 Hz, 1H, H-5); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ ppm: 18.71 (C-9), 32.54 (C-11), 54.89 (C-14, 14′), 58.05 (C-13), 67.57 (C-15, 15′), 68.02 (C-12), 109.70 (C-6), 112.99 (C-3), 114.89 (C-4a), 120.58 (C-8), 127.76 (C-5), 151.40 (C-8a), 153.65 (C-4), 158.75 (C-7), 160.06 (C-2), 199.19 (C-10). TOF MS ES+: $[M + H]^+$ calcd for $C_{18}H_{22}NO_5$: 332.1498 found 332.1534.

*4.2.21. 6-Acetyl-7-[2-piperidylethoxy]4-methylchromen-2-one (**6c**)*

M.p.: 120.5–121 °C (cyclohexane); eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt–MeOH 10:3:1:1), R_f (**6c**) = 0.18; IR (KBr) cm^{-1}: 3059 ($\nu_{C-Harom}$), 2932 ($\nu_{C-Hasym}$), 2851 (ν_{C-Hsym}), 1730, 1667 ($\nu_{C=O}$), 1605, 1496, 1453 ($\nu_{C=C}$), 1466 ($\delta_{C-Hasym}$), 1387 (δ_{C-Hsym}), 1281 ($\nu_{C-O-Casym}$), 1057 ($\nu_{C-O-Csym}$), 834 (γ_{C-H}); ^1H NMR (300 MHz, $(CD_3)_2CO$) δ ppm: 1.44 (m, 2H, H-16), 1.55 (m, 4H, H-15, 15′), 2.47 (d, J = 1.0 Hz, 3H, H-9), 2.51 (bt, J = 5.0 Hz, 4H, H-14, 14′), 2.65 (s, 3H, H-11), 2.83 (t, J = 5.7 Hz, 2H, H-13), 4.37 (t, J = 5.7 Hz, 2H, H-12), 6.19 (bq, J = 1.0 Hz, 1H, H-3), 7.05 (s, 1H, H-8), 8.00 (s, 1H, H-5); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ ppm: 18.89 (C-9), 24.09 (C-16), 25.90 (C-15, 15′), 32.23 (C-11), 55.19 (C-14, 14′), 57.50 (C-13), 67.33 (C-12), 100.87 (C-8), 113.11 (C-3), 113.72 (C-4a), 125.26 (C-6), 128.10 (C-5), 152.88 (C-4), 157.75 (C-8a), 160.51 (C-2), 161.15 (C-7), 197.96 (C-10). TOF MS ES+: $[M + H]^+$ calcd for $C_{19}H_{24}NO_4$: 330.1705 found 330.1713.

*4.2.22. 8-Acetyl-7-[2-piperidylethoxy]4-methylchromen-2-one (**6d**)*

M.p.: 93–93.5 °C (cyclohexane); eluent used in TLC: ($CHCl_3$–$(CH_3)_2CO$–AcOEt–MeOH 10:3:1:1), R_f (**6d**) = 0.14; IR (KBr) cm^{-1}: 3092 ($\nu_{C-Harom}$), 2933 ($\nu_{C-Hasym}$), 2847 (ν_{C-Hsym}), 1727, 1704 ($\nu_{C=O}$), 1599, 1565, 1496 ($\nu_{C=C}$), 1474 ($\delta_{C-Hasym}$), 1386 (δ_{C-Hsym}), 1295 ($\nu_{C-O-Casym}$), 1098 ($\nu_{C-O-Csym}$), 848 (γ_{C-H}); ^1H NMR (500 MHz, $(CD_3)_2CO$) δ ppm: 1.41 (br. quintet 2H, H-16), 1.53 (quintet, J = 5.5 Hz, 4H, H-15, 15′), 2.45 (s, J = 1.5 Hz, 3H, H-9), 2.46 (m, 4H, H-14, 14′), 2.55 (s, 3H, H-11), 2.71 (t, J = 5.5 Hz, 2H, H-13), 4.27 (t, J = 5.5 Hz, 2H, H-12), 6.15 (bq, J = 1.5 Hz, 1H, H-3), 7.14 (d, J = 9.0 Hz 1H, H-6), 7.76 (s, J = 9.0 Hz 1H, H-5); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ ppm: 18.63 (C-9), 25.02 (C-16), 26.89 (C-15, 15′), 32.43 (C-11), 55.59 (C-14, 14′), 58.29 (C-13), 68.24 (C-12), 109.62 (C-6), 112.84 (C-3), 114.72 (C-4a), 120.45 (C-8), 127.66 (C-5), 151.29 (C-8a), 153.57 (C-4), 158.77 (C-7), 159.99 (C-2), 199.11 (C-10). TOF MS ES+: $[M + H]^+$ calcd for $C_{19}H_{24}NO_4$: 330.1705 found 330.1737.

*4.3. General procedure for the preparation hydrochlorides of coumarin derivatives **1ah–dh**, **2bh–dh**, **3ah–dh**, **4ah–dh**, **5ah–bh**, **6ch–dh***

Compounds **1a–d**, **2b–d**, **3a–d**, **4a–d**, **5a–b**, **6c–d** (1.0 mmol) was dissolved in anhydrous ethanol (4–10 mL) and 2–3 mL of anhydrous ethanol saturated with gaseous hydrochloride was added dropwise. The mixture was heated to boiling and then stirred at room temperature for 15–30 min. The mixture was then poured out into a flask with diethyl ether (100 mL) and the precipitate was filtered out and dried.

*4.3.1. 7-[2-(N,N-Diisopropylamino)ethoxy]chromen-2-one hydrochloride (**1ah**)*

Yield 96%; m.p.: 183–183.3 °C; $C_{17}H_{23}NO_3 \cdot HCl$ (325.84 g/mol): calcd. C 62.67%; H 7.42%; N 4.30%; Cl 10.88%; found C 62.75%; H 7.34%; N 4.28%; Cl 10.79%; IR (KBr) cm^{-1}: 3077 ($\nu_{C-Harom}$), 2981 ($\nu_{C-Hasym}$), 2876 (ν_{C-Hsym}), 2700–2300 (ν_{N^+-H}), 1718 ($\nu_{C=O}$), 1612, 1506, 1457 ($\nu_{C=C}$), 1478 ($\delta_{C-Hasym}$), 1397 (δ_{C-Hsym}), 1274 ($\nu_{C-O-Casym}$), 1056 ($\nu_{C-O-Csym}$), 848 (γ_{C-H}); ^1H NMR (300 MHz, $(CD_3)_2CO$) δ ppm: 1.45, 1.47 (2d, J = 6.6 Hz, 12H, H-15, 15′), 3.68 (t, J = 4.8 Hz, 2H, H-13), 3.85 (heptet, J = 6.6 Hz, 2H, H-14, 14′), 4.43 (t, J = 4.8 Hz, 2H, H-12), 6.29 (d, J = 9.6 Hz, 1H, H-3), 7.01 (d, J = 2.4 Hz, 1H, H-8), 7.02 (dd, J_1 = 2.4 Hz, J_2 = 9.0 Hz, 1H, H-6), 7.60 (d, J = 9.0 Hz, 1H, H-5), 7.91 (d, J = 9.6 Hz, 1H, H-4); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ ppm: 17.38, 19.24 (C-15, 15′), 48.21 (C-13), 57.77 (C-14, 14′), 66.26 (C-12), 102.82 (C-8), 114.07 (C-6), 114.40 (C-3), 115.08 (C-4a), 130.93 (C-5), 145.66 (C-4), 157.18 (C-8a), 162.42 (C-7), 163.12 (C-2).

*4.3.2. 7-[2-(N,N-Diisopropylamino)ethoxy]4-methylchromen-2-one hydrochloride (**1bh**)*

Yield 94%; m.p.: 188.5–190 °C; $C_{18}H_{25}NO_3 \cdot HCl$ (339.86 g/mol): calcd. C 63.61,H 7.71, N 4.12, Cl 10.43%; found C 63.47, H 7.73, N 4.20, Cl 10.32%; IR (KBr) cm^{-1}: 3023 ($\nu_{C-Harom}$), 2974 ($\nu_{C-Hasym}$), 2875 (ν_{C-Hsym}), 2650–2300 (ν_{N^+-H}), 1706 ($\nu_{C=O}$), 1610, 1510 ($\nu_{C=C}$), 1465 ($\delta_{C-Hasym}$), 1388 (δ_{C-Hsym}), 1283 ($\nu_{C-O-Casym}$), 1073 ($\nu_{C-O-Csym}$), 844 (γ_{C-H}); ^1H NMR (300 MHz, CD_3OD) δ ppm: 1.45, 1.48 (2d, J = 6.6 Hz, 12H, H-15, 15′), 2.46 (d, J = 0.9 Hz, 3H, H-9), 3.69 (bt, J = 4.8 Hz, 2H, H-13), 3.85 (heptet, J = 6.6 Hz, 2H, H-14, 14′), 4.44 (bt, J = 4.8 Hz, 2H, H-12), 6.20 (bq, J = 0.9 Hz, 1H, H-3), 7.00 (d, J = 2.3 Hz, 1H, H-8), 7.04 (dd, J_1 = 8.8 Hz, J_2 = 2.3 Hz, 1H, H-6), 7.65 (d, J = 8.8 Hz, 1H, H-5); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 17.39, 19.24 (C-15, 15′), 48.22 (C-13),

57.76 (C-14, 14′), 66.23 (C-12), 102.86 (C-8), 112.97 (C-3), 113.87 (C-6), 115.86 (C-4a), 127.80 (C-5), 155.64 (C-4), 156.52 (C-8a), 162.32 (C-7), 163.34 (C-2).

4.3.3. 6-Acetyl-7-[2-(N,N-diisopropylamino)ethoxy]4-methylchromen-2-one hydrochloride (**1ch**)

Yield 98%; m.p.: 202.7–203.5 °C; $C_{20}H_{27}NO_4 \cdot HCl \cdot H_2O$ (399.92 g/mol): calcd. C 60.07, H 7.56, N 3.50, Cl 8.87%; found C 59.18, H 7.18, N 3.52, Cl 8.54%; IR (KBr) cm^{-1}: 3035 ($\nu_{C-Harom}$), 2977 ($\nu_{C-Hasym}$), 2874 (ν_{C-Hsym}), 2650–2350 (ν_{N^+-H}), 1726 ($\nu_{C=O}$), 1617, 1601, 1495 ($\nu_{C=C}$), 1466 ($\delta_{C-Hasym}$), 1386 (δ_{C-Hsym}), 1281 ($\nu_{C-O-Casym}$), 1061 ($\nu_{C-O-Csym}$), 889 (γ_{C-H}); ^{1}H NMR (300 MHz, CD_3OD) δ ppm: 1.45, 1.46 (2d, $J = 6.6$ Hz, 12H, H-15, 15′), 2.51 (d, $J = 1.2$ Hz, 3H, H-9), 2.69 (s, 3H, H-11), 3.74 (t, $J = 5.1$ Hz, 2H, H-13), 3.94 (heptet, $J = 6.6$ Hz, 2H, H-14, 14′), 4.57 (t, $J = 5.1$ Hz, 2H, H-12), 6.29 (bq, $J = 1.2$ Hz, 1H, H-3), 7.18 (s, 1H, H-8), 8.14 (s, 1H, H-5); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 17.82 (C-15), 18.67 (C-9), 19.07 (C-15′), 30.82 (C-11), 47.23 (C-13), 57.07 (C-14, 14′), 66.52 (C-12), 103.36 (C-8), 114.15 (C-3), 115.55 (C-4a), 126.61 (C-6), 129.51 (C-5), 155.12 (C-4), 158.69 (C-8a), 160.63 (C-7), 162.20 (C-2), 200.87 (C-10).

4.3.4. 8-Acetyl-7-[2-(N,N-diisopropylamino)ethoxy]4-methylchromen-2-one hydrochloride (**1dh**)

Yield 91%; m.p.: 221.3–222 (dec.) °C; $C_{20}H_{27}NO_4 \cdot HCl \cdot H_2O$ (399.92 g/mol): calcd. C 60.07, H 7.56, N 3.50, Cl 8.87%; found C 60.20, H 7.14, N 3.68, Cl 8.74%; IR (KBr) cm^{-1}: 3037 ($\nu_{C-Harom}$), 2980 ($\nu_{C-Hasym}$), 2878 (ν_{C-Hsym}), 2650–2350 (ν_{N^+-H}), 1731, 1699 ($\nu_{C=O}$), 1601, 1566, 1441 ($\nu_{C=C}$), 1466 ($\delta_{C-Hasym}$), 1377 (δ_{C-Hsym}), 1292 ($\nu_{C-O-Casym}$), 1105 ($\nu_{C-O-Csym}$), 891 (γ_{C-H}); ^{1}H NMR (300 MHz, CD_3OD) δ ppm: 1.43 (d, $J = 6.6$ Hz, 12H, H-15, 15′), 2.48 (d, $J = 1.2$ Hz, 3H, H-9), 2.63 (s, 3H, H-11), 3.68 (t, $J = 4.8$ Hz, 2H, H-13), 3.85 (heptet, $J = 6.6$ Hz, 2H, H-14, 14′), 4.50 (t, $J = 4.8$ Hz, 2H, H-12), 6.26 (bq, $J = 1.2$ Hz, 1H, H-3), 7.19 (d, $J = 9.0$ Hz, 1H, H-6), 7.87 (d, $J = 9.0$ Hz, 1H, H-5); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 17.51 (C-9), 18.90 (C-15, 15′), 33.04 (C-11), 47.89 (C-13), 57.41 (C-14, 14′), 67.11 (C-12), 110.43 (C-6), 113.59 (C-3), 116.26 (C-4a), 120.42 (C-8), 129.06 (C-5), 152.20 (C-8a), 155.29 (C-4), 157.90 (C-7), 161.88 (C-2), 202.21 (C-10).

4.3.5. 7-[2-(N-Benzyl-N-methylamino)ethoxy]4-methylchromen-2-one hydrochloride (**2bh**)

Yield 83%; m.p.: 168.2–169.2 °C; $C_{20}H_{21}NO_3 \cdot HCl \cdot 1/2H_2O$ (368.86 g/mol): calcd. C 65.12, H 6.28, N 3.80, Cl 9.61%; found C 65.17, H 6.20, N 3.79, Cl 9.59%; IR (KBr) cm^{-1}: 3037 ($\nu_{C-Harom}$), 2951 ($\nu_{C-Hasym}$), 2882 (ν_{C-Hsym}), 2700–2300 (ν_{N^+-H}), 1733, 1700 ($\nu_{C=O}$), 1616, 1511, 1496 ($\nu_{C=C}$), 1458 ($\delta_{C-Hasym}$), 1389 (δ_{C-Hsym}), 1294 ($\nu_{C-O-Casym}$), 1073 ($\nu_{C-O-Csym}$), 844 (γ_{C-H}); ^{1}H NMR (300 MHz, CD_3OD) δ ppm: 2.47 (d, $J = 1.0$ Hz, 3H, H-9), 2.96 (s, 3H, H-14), 3.66 (bs, 2H, H-13), 4.47 (bs, 2H, H-15), 4.50 (t, $J = 5.1$ Hz, 2H, H-12), 6.22 (bq, $J = 1.0$ Hz, 1H, H-3), 7.00 (d, $J = 2.4$ Hz, 1H, H-8), 7.05 (dd, $J_1 = 2.4$ Hz, $J_2 = 9.0$ Hz, 1H, H-6), 7.49–7.57 (m, 5H, H-17, 17′, 18, 18′, 19), 7.75 (d, $J = 9.0$ Hz, 1H, H-5); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 18.77 (C-9), 41.41 (C-14), 55.70 (C-13), 61.77 (C-15), 63.93 (C-12), 103.05 (C-8), 113.03 (C-6), 113.87 (C-3), 115.96 (C-4a), 127.77 (C-5), 130.65 (C-17, 17′), 131.52 (C-16, 19), 132.43 (C-18, 18′), 155.58 (C-4), 156.47 (C-8a), 162.20 (C-7), 163.30 (C-2).

4.3.6. 6-Acetyl-7-[2-(N-benzyl-N-methylamino)ethoxy]4-methylchromen-2-one hydrochloride (**2ch**)

Yield 92%; m.p.: 208–208.5 (dec.) °C; $C_{22}H_{23}NO_4 \cdot HCl \cdot H_2O$ (410.90 g/mol): calcd. C 64.31, H 6.13, N 3.41, Cl 8.63%; found C 64.59, H 6.13, N 3.55, Cl 8.54%; IR (KBr) cm^{-1}: 3043 ($\nu_{C-Harom}$), 2933 ($\nu_{C-Hasym}$), 2870 (ν_{C-Hsym}), 2700–2300 (ν_{N^+-H}), 1716, 1676 ($\nu_{C=O}$), 1601, 1497, 1450 ($\nu_{C=C}$), 1465 ($\delta_{C-Hasym}$), 1388 (δ_{C-Hsym}), 1283 ($\nu_{C-O-Casym}$), 1058 ($\nu_{C-O-Csym}$), 826 (γ_{C-H}); ^{1}H NMR (300 MHz, CD_3OD) δ ppm: 2.49 (d, $J = 1.0$ Hz, 3H, H-9), 2.57 (s, 3H, H-11), 3.01 (s, 3H, H-14), 3.64, 3.82 (2 × m, 2H, H-13), 4.47, 4.59 (2 × d, $J = 12.6$ Hz, 2H, H-15), 4.61 (m, 2H, H-12), 6.29 (bq, $J = 1.0$ Hz, 1H, H-3), 7.14 (s, 1H, H-8), 7.50–7.59 (m, 5H, H-17, 17′, 18, 18′, 19), 8.12 (s, 1H, H-5); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 18.66 (C-9), 31.21 (C-11), 41.47 (C-14), 55.79 (C-13), 62.15 (C-15), 65.19 (C-12), 103.02 (C-8), 114.10 (C-3), 115.54 (C-4a), 126.74 (C-6), 129.41 (C-5), 130.74 (C-16, 17, 17′), 131.67 (C-19), 132.48 (C-18, 18′), 155.16 (C-4), 158.69 (C-8a), 160.78 (C-7), 162.24 (C-2), 200.12 (C-10).

4.3.7. 8-Acetyl-7-[2-(N-benzyl-N-methylamino)ethoxy]4-methylchromen-2-one hydrochloride (**2dh**)

Yield 54%; hygroscopic compound; $C_{22}H_{23}NO_4 \cdot HCl \cdot H_2O$ (419.91 g/mol): calcd. C 62.93, H 6.24, N 3.34, Cl 8.44%; found C 63.03, H 6.35, N 3.38, Cl 8.39%; IR (KBr) cm^{-1}: 3033 ($\nu_{C-Harom}$), 2954 ($\nu_{C-Hasym}$), 2880 (ν_{C-Hsym}), 2700–2300 (ν_{N^+-H}), 1730, 1705 ($\nu_{C=O}$), 1599, 1495 ($\nu_{C=C}$), 1458 ($\delta_{C-Hasym}$), 1384 (δ_{C-Hsym}), 1291 ($\nu_{C-O-Casym}$), 1105 ($\nu_{C-O-Csym}$), 746 (γ_{C-H}); ^{1}H NMR (300 MHz, CD_3OD) δ ppm: 2.47 (d, $J = 0.9$ Hz, 3H, H-9), 2.59 (s, 3H, H-11), 2.93 (s, 3H, H-14), 3.64, 3,71 (2 × m, 2H, H-13), 4.40, 4.55 (2 × d, $J = 12.3$ Hz, 2H, H-15), 4.60 (m, 2H, H-12), 6.25 (bq, $J = 0.9$ Hz, 1H, H-3), 7.19 (d, $J = 9.0$ Hz, 1H, H-6), 7.50–7.59 (m, 5H, H-17, 17′, 18, 18′, 19), 7.85 (d, $J = 9.0$ Hz, 1H, H-5); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 18.90 (C-9), 32.90 (C-11), 41.45 (C-14), 55.87 (C-13), 61.98 (C-15), 65.35 (C-12), 110.78 (C-6), 113.62 (C-3), 116.32 (C-4a), 120.68 (C-8), 129.04 (C-5), 130.67 (C-17, 17′), 130.83 (C-16), 131.53 (C-19), 132.41 (C-18, 18′), 152.13 (C-4), 155.21 (C-8a), 157.83 (C-7), 161.79 (C-2), 201.83 (C-10).

4.3.8. 7-[2-(N,N-Diethylamino)ethoxy]chromen-2-one hydrochloride (**3ah**)

Yield 96%; m.p.: 183–184 °C (Lit. m.p.: 174–175 °C [17]). $C_{15}H_{19}NO_3 \cdot HCl$ (297.78 g/mol): calcd. C 60.50, H 6.77, N 4.70, Cl 11.91%; found C 60.77, H 6.76, N 4.72, Cl 12.06%; IR (KBr) cm^{-1}: 3037 ($\nu_{C-Harom}$), 2945 ($\nu_{C-Hasym}$), 2885 (ν_{C-Hsym}), 2700–2300 (ν_{N^+-H}), 1726, 1708 ($\nu_{C=O}$), 1627, 1506, 1445 ($\nu_{C=C}$), 1468 ($\delta_{C-Hasym}$), 1380 (δ_{C-Hsym}), 1295 ($\nu_{C-O-Casym}$), 1032 ($\nu_{C-O-Csym}$), 838 (γ_{C-H}); ^{1}H NMR (300 MHz, CD_3OD) δ ppm: 1.39 (t, $J = 7.2$ Hz, 6H, H-15, 15′), 3.36 (dq, $J_1 = 7.2$ Hz, $J_2 = 3.3$ Hz, 4H, H-14, 14′), 3.67 (bt, $J = 4.8$ Hz, 2H, H-13), 4.48 (bt, $J = 4.8$ Hz, 2H, H-12), 6.30 (d, $J = 9.6$ Hz, 1H, H-3), 7.03 (bs, 1H, H-8), 7.04 (dd, $J_1 = 2.4$ Hz, $J_2 = 9.4$ Hz, 1H, H-6), 7.61 (d, $J = 9.6$ Hz, 1H, H-5), 7.91 (d, $J = 9.6$ Hz, 1H, H-4); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 9.28 (C-15, 15′), 49.64 (C-14, 14′), 52.27 (C-13), 64.14 (C-12), 103.01 (C-8), 114.08 (C-6), 114.42 (C-3), 115.13 (C-4a), 130.90 (C-5), 145.65 (C-4), 157.12 (C-8a), 162.37 (C-7), 163.10 (C-2).

4.3.9. 7-[2-(N,N-Diethylamino)ethoxy]4-methylchromen-2-one hydrochloride (**3bh**)

Yield 92%; m.p.: 215–216 °C (Lit. 213–215 °C [19]); $C_{16}H_{21}NO_3 \cdot HCl$ (311.81 g/mol): calcd. C 61.63, H 7.11, N 4.49, Cl 11.37%; found C 61.32, H 6.93, N 4.53, Cl 11.16%; IR (KBr) cm^{-1}: 3054 ($\nu_{C-Harom}$), 2974 ($\nu_{C-Hasym}$), 2885 (ν_{C-Hsym}), 2650–2300 (ν_{N^+-H}), 1720 broad ($\nu_{C=O}$), 1609, 1510, 1443 ($\nu_{C=C}$), 1463 ($\delta_{C-Hasym}$), 1389 (δ_{C-Hsym}), 1283 ($\nu_{C-O-Casym}$), 1070 ($\nu_{C-O-Csym}$), 834 (γ_{C-H}); ^{1}H NMR (300 MHz, CD_3OD) δ ppm: 1.39 (t, $J = 7.2$ Hz, 6H, H-15, 15′), 2.46 (d, $J = 1.2$ Hz, 3H, H-9), 3.37 (dq, $J_1 = 7.2$ Hz, $J_2 = 2.4$ Hz, 4H, H-14, 14′), 3.67 (t, $J = 5.1$ Hz, 2H, H-13), 4.48 (t, $J = 5.1$ Hz, 2H, H-12), 6.22 (bq, $J = 1.2$ Hz, 1H, H-3), 7.03 (d, $J = 2.4$ Hz, 1H, H-8), 7.07 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.7$ Hz, 1H, H-6), 7.75 (d, $J = 8.7$ Hz, 1H, H-5); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 9.27 (C-15, 15′), 18.77 (C-9), 49.64 (C-14, 14′), 52.29 (C-13), 64.09 (C-12), 103.02 (C-8), 113.03 (C-3), 113.85 (C-6), 115.94 (C-4a), 127.78 (C-5), 155.57 (C-4), 156.48 (C-8a), 162.26 (C-7), 163.29 (C-2).

*4.3.10. 6-Acetyl-7-[2-(N,N-diethylamino)ethoxy]4-methylchromen-2-one hydrochloride (**3ch**)*

Yield 73%; m.p.: 220.5–221 (dec.) °C. $C_{18}H_{23}NO_4 \cdot HCl$ (353.85 g/mol): calcd. C 61.10, H 6.84, N 3.96, Cl 10.02%; found C 60.97, H 6.80, N 3.99, Cl 10.05%; IR (KBr) cm^{-1}: 3071 ($\nu_{C-Harom}$), 2966 ($\nu_{C-Hasym}$), 2885 (ν_{C-Hsym}), 2650–2300 (ν_{N^+-H}), 1733 broad, 1679 ($\nu_{C=O}$), 1600, 1497, ($\nu_{C=C}$), 1459 ($\delta_{C-Hasym}$), 1386 (δ_{C-Hsym}), 1285 ($\nu_{C-O-Casym}$), 1062 ($\nu_{C-O-Csym}$), 894 (γ_{C-H}); ^1H NMR (300 MHz, CD_3OD) δ ppm: 1.39, 1.41 (2d, $J = 7.2$ Hz, 6H, H-15, 15′), 2.50 (d, $J = 0.9$ Hz, 3H, H-9), 2.68 (s, 3H, H-11), 3.40, 3.44 (2q, $J = 7.2$ Hz, 4H, H-14, 14′), 3.73 (t, $J = 4.8$ Hz, 2H, H-13), 4.59 (t, $J = 4.8$ Hz, 2H, H-12), 6.29 (bq, $J = 0.9$ Hz, 1H, H-3), 7.18 (s, 1H, H-8), 8.13 (s, 1H, H-5); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 9.41 (C-15, 15′), 18.66 (C-9), 31.11 (C-11), 49.79 (C-14, 14′), 52.52 (C-13), 65.41 (C-12), 103.06 (C-8), 114.09 (C-3), 115.50 (C-4a), 126.77 (C-6), 129.39 (C-5), 155.16 (C-4), 158.67 (C-8a), 160.80 (C-7), 162.26 (C-2), 200.24 (C-10).

*4.3.11. 8-Acetyl-7-[2-(N,N-diethylamino)ethoxy]4-methylchromen-2-one hydrochloride (**3dh**)*

Yield 92%; m.p.: 213–213.5 °C; $C_{18}H_{23}NO_4 \cdot HCl$ (353.85 g/mol): calcd. C 61.10, H 6.84, N 3.96, Cl 10.02%; found C 60.98, H 6.77, N 4.03, Cl 9.91%; IR (KBr) cm^{-1}: 3084 ($\nu_{C-Harom}$), 2974 ($\nu_{C-Hasym}$), 2878 (ν_{C-Hsym}), 2700–2300 (ν_{N^+-H}), 1711 ($\nu_{C=O}$), 1603, 1564, 1494, 1445 ($\nu_{C=C}$), 1461 ($\delta_{C-Hasym}$), 1388 (δ_{C-Hsym}), 1292 ($\nu_{C-O-Casym}$), 1106 ($\nu_{C-O-Csym}$), 861 (γ_{C-H}); ^1H NMR (300 MHz, CD_3OD) δ ppm: 1.37 (t, $J = 7.2$ Hz, 6H, H-15, 15′), 2.48 (d, $J = 1.2$ Hz, 3H, H-9), 2.63 (s, 3H, H-11), 3.35 (q, $J = 7.2$ Hz, 4H, H-14, 14′), 3.66 (t, $J = 4.8$ Hz, 2H, H-12), 4.54 (t, $J = 4.8$ Hz, 2H, H-13), 6.27 (d, $J = 1.2$ Hz, 1H, H-3), 7.20 (d, $J = 9.0$ Hz, 1H, H-6), 7.87 (d, $J = 9.0$ Hz, 1H, H-5); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 9.50 (C-15, 15′), 18.89 (C-9), 32.92 (C-11), 50.07 (C-14, 14′), 52.23 (C-13), 65.57 (C-12), 110.56 (C-6), 113.64 (C-3), 116.33 (C-4a), 120.62 (C-8), 129.03 (C-5), 152.16 (C-8a), 155.21 (C-4), 157.87 (C-7), 161.79 (C-2), 201.78 (C-10).

*4.3.12. 7-[2-(2-Methylpiperidinyl)ethoxy]chromen-2-one hydrochloride (**4ah**)*

Yield 85%; m.p.: 171.5–172 °C. $C_{17}H_{21}NO_3 \cdot HCl$ (323.82 g/mol): calcd. C 63.06, H 6.85, N 4.33, Cl 10.95%; found C 63.06, H 6.86, N 4.32, Cl 11.11%; IR (KBr) cm^{-1}: 3034 ($\nu_{C-Harom}$), 2939 ($\nu_{C-Hasym}$), 2864 (ν_{C-Hsym}), 2700–2300 (ν_{N^+-H}), 1725, 1706 ($\nu_{C=O}$), 1626, 1554, 1505, ($\nu_{C=C}$), 1458 ($\delta_{C-Hasym}$), 1356 (δ_{C-Hsym}), 1296 ($\nu_{C-O-Casym}$), 1016 ($\nu_{C-O-Csym}$), 838 (γ_{C-H}); ^1H NMR (300 MHz, CD_3OD) δ ppm: 1.48 (d, $J = 6.0$ Hz, 3H, H-19), 1.60–2.10 (m, 6H, H-15, 16, 17), 3.16 (m, 1H, Hax-18), 3.38 (m, 1H, H-14), 3.59 (m, 1H, Hax-13), 3.70 (m, 1H, Heq-18), 3.88 (m, 1H, Heq-13), 4.47 (m, 1H, H-12), 6.30 (d, $J = 9,6$ Hz, 1H, H-3), 7.03 (bd, $J = 2.7$ Hz, 1H, H-8), 7.04 (dd, $J_1 = 8.6$ Hz, $J_2 = 2.7$ Hz, 1H, H-6), 7.61 (d, $J = 8.6$ Hz, 1H, H-5), 7.91 (d, $J = 9.6$ Hz, 1H, H-4); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 18.51 (C-9), 23.05 (C-16), 24.51 (C-17), 33.01 (C-15), 53.81 (C-13), 54.61 (C-18), 62.41 (C-14), 63.90 (C-12), 102.96 (C-8), 114.09 (C-6), 114.44 (C-3), 115.13 (C-4a), 130.90 (C-5), 145.64 (C-4), 157.16 (C-8a), 162.41 (C-2), 163.13 (C-7).

*4.3.13. 7-[2-(2-Methylpiperidinyl)ethoxy]4-methylchromen-2-one hydrochloride (**4bh**)*

Yield 99%; m.p.: 229–230 (dec.) °C; $C_{18}H_{23}NO_3 \cdot HCl \cdot 1/2H_2O$ (346.86 g/mol): calcd. C 62.33, H 7.26, N 4.04, Cl 10.22%; found C 62.35, H 7.13, N 4.08, Cl 10.25%; IR (KBr) cm^{-1}: 3092, 3035 ($\nu_{C-Harom}$), 2940 ($\nu_{C-Hasym}$), 2860 (ν_{C-Hsym}), 2700–2300 (ν_{N^+-H}), 1710 ($\nu_{C=O}$), 1624, 1616, 1510 ($\nu_{C=C}$), 1450 ($\delta_{C-Hasym}$), 1392 (δ_{C-Hsym}), 1297 ($\nu_{C-O-Casym}$), 1017 ($\nu_{C-O-Csym}$), 838 (γ_{C-H}); Diastereoisomers: ^1H NMR (300 MHz, CD_3OD) δ ppm: 1.46, 1.50 (2d, $J = 6.6$ Hz, 3H, H-19), 1.61–2.08 (m, 6H, H-15, 16, 17), 2.47 (2, $J = 1.0$ Hz, 3H, H-9), 3.16 (m, 1H, Hax-18), 3.39 (m, 1H, H-14), 3.52–3.59 (m, 1H, Hax-13), 3.71 (bm, 1H, Heq-18), 3.86–3.95 (m, 1H, Heq-13), 4.45–4.58 (m, 2H, H-12), 6.22 (bq, $J = 1.0$ Hz, 1H, H-3), 7.03 (d, $J = 2,7$ Hz, 1H, H-8), 7.08 (dd, $J_1 = 9.0$ Hz, $J_2 = 2.7$ Hz, 1H, H-6), 7.76 (d, $J = 9.0$ Hz, 1H, H-5); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 18.78 (C-9), 14.24, 18.49, 20.11, 23.05, 21.76, 24.48, 28.84, 33.01 (C-19, C-16, C-17, C-15), 50.78, 53.79, 54.62, 59,34, 62.40, 63.87 64.30 (C-13, C-18, C-14, C-12), 103.00 (C-8), 112.98 (C-3), 113.89 (C-6), 115.89 (C-4a), 127.76 (C-5), 155.60 (C-4), 156.48 (C-8a), 162.32 (C-7), 163.32 (C-2).

*4.3.14. 6-Acetyl-7-[2-(2-methylpiperidinyl)ethoxy]4-methylchromen-2-one hydrochloride (**4ch**)*

Yield 95%; m.p.: 216–217 (dec.) °C; $C_{20}H_{25}NO_4 \cdot HCl$ (379.88 g/mol): calcd. C 63.24, H 6.90, N 3.69, Cl 9.33%; found C 63.06, H 6.86, N 3.71, Cl 8.96%; IR (KBr) cm^{-1}: 3066 ($\nu_{C-Harom}$), 2941 ($\nu_{C-Hasym}$), 2852 (ν_{C-Hsym}), 2650–2300 (ν_{N^+-H}), 1732, 1675 ($\nu_{C=O}$), 1600, 1498, ($\nu_{C=C}$), 1461 ($\delta_{C-Hasym}$), 1384 (δ_{C-Hsym}), 1282 ($\nu_{C-O-Casym}$), 1057 ($\nu_{C-O-Csym}$), 889 (γ_{C-H}); Diasteroisomers. ^1H NMR (300 MHz, CD_3OD) δ ppm: 1.44, 1.49 (2d, $J = 6.0$ Hz, 3H, H-19), 1.84–2.09 (m, 6H, H-15, 16, 17), 2.49 (bs, 3H, H-9), 2.68 (s, 3H, H-11), 3.21 (m, 1H, Hax-18), 3.45 (m, 1H, H-14), 3.62 (m, 1H, Hax-13), 3.81 (m, 1H, Heq-18), 3.97 (m, 1H, Heq-13), 4.60 (m, 2H, H-12), 6.27 (bs, 1H, H-3), 7.18 (s, 1H, H-8), 8.12 (s, 1H, H-5); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 18.67 (C-9), 31.23 (C-11), 13.77, 18.56, 22.26, 23.03, 24.36, 24.52, 33.06 (C-19, C-16, C-17, C-15), 50.61, 51.89, 53.66, 55.16, 59.55, 62.19, 65.21 (C-13, C-18, C-14, C-12), 102.98 (C-8), 114.03 (C-3), 115.39 (C-4a), 126.74 (C-6), 129.31 (C-5), 155.17 (C-4), 158.66 (C-8a), 160.85 (C-7), 162.28 (C-2), 200.15 (C-10).

*4.3.15. 8-Acetyl-7-[2-(2-methylpiperidinyl)ethoxy]4-methylchromen-2-one hydrochloride (**4dh**)*

Yield 56%; m.p.: 199.8–200.8 (dec.) °C; $C_{20}H_{25}NO_4 \cdot HCl \cdot 11/2H_2O$ (406.91 g/mol): calcd. C 59.04, H 7.18, N 3.44, Cl 8.71%; found C 59.01, H 6.97, N 3.67, Cl 9.07%; IR (KBr) cm^{-1}: 3075 ($\nu_{C-Harom}$), 2950 ($\nu_{C-Hasym}$), 2873 (ν_{C-Hsym}), 2700–2300 (ν_{N^+-H}), 1743, 1702 ($\nu_{C=O}$), 1599, 1453 ($\nu_{C=C}$), 1472 ($\delta_{C-Hasym}$), 1385 (δ_{C-Hsym}), 1286 ($\nu_{C-O-Casym}$), 1101 ($\nu_{C-O-Csym}$), 868 (γ_{C-H}); ^1H NMR (300 MHz, CD_3OD) δ ppm: 1.44, 1.40 (2bd, $J = 6.3$ Hz, 3H, H-19), 1.58-2.12 (m, 6H, H-15, 16, 17), 2.48 (d, $J = 0.6$ Hz, 3H, H-9), 2.63 (s, 3H, H-11), 3.07–3.22 (m, 1H, Hax-18), 3.38 (m, 1H, H-14), 3.55–3.70 (m, Hax-13, Heq-18), 3.74–3.83 (m, 1H, Heq-13), 4.55 (bs, 2H, H-12), 6,27 (bq, $J = 0.6$ Hz, 1H, H-3), 7.20 (d, $J = 9.0$ Hz, 1H, H-6), 7.87 (d, $J = 9.0$ Hz, 1H, H-5); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 18.54 (C-19), 18.88 (C-9), 23.02 (C-17), 24.58 (C-16), 32.91 (C-11), 33.12 (C-15), 53.56 (C-13), 55.34 (C-18), 61.96 (C-14), 65.09 (C-12), 110.50 (C-6), 113.63 (C-3), 115.21 (C-4a), 120.62 (C-8), 129.01 (C-5), 155.20 (C4), 157.88 (C-8a), 161.78 (C-7), 163.32 (C-2), 201.91 (C-10).

*4.3.16. 7-[2-(1-Morpholino)ethoxy]chromen-2-one hydrochloride (**5ah**)*

Yield 91%; m.p.: 231–232 (dec.) °C; $C_{15}H_{17}NO_4 \cdot HCl \cdot 2H_2O$ (347.8 g/mol): calcd. C 51.80, H 6.38, N 4.03, Cl 10.19%; found C 52.20, H 5.92, N 4.15, Cl 9.90%; IR (KBr) cm^{-1}: 3056 ($\nu_{C-Harom}$), 2935 ($\nu_{C-Hasym}$), 2868 (ν_{C-Hsym}), 2700–2300 (ν_{N^+-H}), 1727, 1705 ($\nu_{C=O}$), 1609, 1507, 1451 ($\nu_{C=C}$), 1460 ($\delta_{C-Hasym}$), 1355 (δ_{C-Hsym}), 1299 ($\nu_{C-O-Casym}$), 1038 ($\nu_{C-O-Csym}$), 836 (γ_{C-H}); ^1H NMR (300 MHz, CD_3OD) δ ppm: 3.30 (bm, 2H, H-14), 3.58 (bm, 2H, H-14′), 3.70 (bt, $J = 4.8$ Hz, 2H, H-13), 3.90 (bm, 2H, H-15), 4.06 (bm, 2H, H-15′), 4.53 (bt, $J = 4.8$ Hz, 2H, H-12), 6.29 (d, $J = 9.3$ Hz, 1H, H-3), 7.03 (d, $J = 2.4$ Hz, 1H, H-8), 7.05 (dd, $J_1 = 8.5$ Hz, $J_2 = 2.4$ Hz, 1H, H-6), 7.60 (d, $J = 8.5$ Hz, 1H, H-5), 7.90 (d, $J = 9.3$ Hz, 1H, H-4); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 53.92 (C-14, 14′), 57.44 (C-13), 63.68 (C-12), 65.05 (C-15, 15′), 103.06 (C-8), 114.10 (C-6), 114.42 (C-3), 115.14 (C-4a), 130.88 (C-5), 145.64 (C-4), 157.11 (C-8a), 162.34 (C-7), 163.11 (C-2).

*4.3.17. 7-[2-(1-Morpholino)ethoxy]4-methylchromen-2-one hydrochloride (**5bh**)*

Yield 77%; m.p.: 199–199.5 (dec.) °C; $C_{16}H_{19}NO_4 \cdot HCl \cdot 21/2H_2O$ (370.83 g/mol): calcd. C 51.82, H 6.80, N 3.78, Cl 9.56%; found C 52.30, H 6.79, N 3.81, Cl 9.74%; IR (KBr) cm^{-1}: 3040 ($\nu_{C-Harom}$), 2935 ($\nu_{C-Hasym}$), 2868 (ν_{C-Hsym}), 2700–2300 (ν_{N^+-H}), 1707 ($\nu_{C=O}$), 1622, 1510 ($\nu_{C=C}$), 1442 ($\delta_{C-Hasym}$), 1392 (δ_{C-Hsym}), 1296 ($\nu_{C-O-Casym}$), 1067 ($\nu_{C-O-Csym}$), 838 (γ_{C-H}); ^{1}H NMR (300 MHz, CD_3OD) δ ppm: 2.46 (d, J = 1.2 Hz, 3H, H-9), 3.31 (bm, 2H, H-14), 3.58–3.66 (bm, 2H, H-14′), 3.71 (bt, J = 4.8 Hz, 2H, H-13), 3.82-3.90 (bm, 2H, H-15), 4.07–4.11 (bm, 2H, H-15′), 4.53 (bt, J = 4.8 Hz, 2H, H-12), 6.21 (d, J = 1.2 Hz, 1H, H-3), 7.03 (d, J = 2.4 Hz, 1H, H-8), 7.08 (dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz, 1H, H-6), 7.74 (d, J = 8.7 Hz, 1H, H-5); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 18.76 (C-9), 53.91 (C-14, 14′), 57.44 (C-13), 63.59 (C-12), 65.03 (C-15, 15′), 103.08 (C-8), 113.02 (C-3), 113.86 (C-6), 115.94 (C-4a), 127.75 (C-5), 155.57 (C-4), 156.45 (C-8a), 162.22 (C-7), 163.29 (C-2).

*4.3.18. 6-Acetyl-7-[2-piperidylethoxy]4-methylchromen-2-one hydrochloride (**6ch**)*

Yield 95%: m.p.: 227–229 (dec.) °C; $C_{19}H_{23}NO_4 \cdot HCl \cdot H_2O$ (374.86 g/mol): calcd. C 60.88, H 6.72, N 3.74, Cl 9.46%, found C 60.97, H 6.77, N 3.69, Cl 8.76%; IR (KBr) cm^{-1}: 3025 ($\nu_{C-Harom}$), 2949 ($\nu_{C-Hasym}$), 2878 (ν_{C-Hsym}), 2700–2300 (ν_{N^+-H}), 1731, 1672 ($\nu_{C=O}$), 1600, 1497, 1447 ($\nu_{C=C}$), 1465 ($\delta_{C-Hasym}$), 1365 (δ_{C-Hsym}), 1287 ($\nu_{C-O-Casym}$), 1062 ($\nu_{C-O-Csym}$), 844 (γ_{C-H}); ^{1}H NMR (300 MHz, CD_3OD) δ ppm: 1.57 (bm, 1H, Hax-16), 1.81–2.03 (m, 5H, Heq-16, H-15, 15′), 2.50 (d, J = 1.0 Hz, 3H, H-9), 2.68 (s, 3H, H-11), 3.10 (bm, 2H, H-14), 3.68 (bt, J = 4.8 Hz, 2H, H-13), 3.73 (bs, 2H, H-14′), 4.60 (bt, J = 4.8 Hz, 2H, H-12), 6.28 (d, J = 1.0 Hz, 1H, H-3), 7.17 (s, 1H, H-8), 8.14 (s, 1H, H-5); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 18.66 (C-9), 22.63 (C-16), 24.43 (C-15, 15′), 31.17 (C-11), 55.39 (C-14,14′), 57.17 (C-13), 65.14 (C-12), 103.07 (C-8), 114.07 (C-3), 115.07 (C-4a), 126.73 (C-6), 129.43 (C-5), 155.17 (C-4), 158.71 (C-8a), 160.86 (C-7), 162.26 (C-2), 200.17 (C-10).

*4.3.19. 8-Acetyl-7-[2-piperidylethoxy]4-methylchromen-2-one hydrochloride (**6dh**)*

Yield 79%; m.p.: 231–233 (dec.) °C; $C_{19}H_{23}NO_4 \cdot HCl \cdot H_2O$ (383.87 g/mol): calcd. C 59.45, H 6.83, N 3.65, Cl 9.24%; found C 59.32, H 6.54, N 3.77, Cl 9.90%; IR (KBr) cm^{-1}: 3076 ($\nu_{C-Harom}$), 2949 ($\nu_{C-Hasym}$), 2863 (ν_{C-Hsym}), 2650–2300 (ν_{N^+-H}), 1744, 1699 ($\nu_{C=O}$), 1599, 1492, 1452 ($\nu_{C=C}$), 1469 ($\delta_{C-Hasym}$), 1385 (δ_{C-Hsym}), 1287 ($\nu_{C-O-Casym}$), 1052 ($\nu_{C-O-Csym}$), 867 (γ_{C-H}); ^{1}H NMR (300 MHz, CD_3OD) δ ppm: 1.59 (bm, 1H, Hax-16), 1.80–2.03 (m, 5H, Heq-16, H-15, 15′), 2.49 (d, J = 1.2 Hz, 3H, H-9), 2.64 (s, 3H, H-11), 3.10 (m, 2H, H-14), 3.61 (bt, J = 4.8 Hz, 2H, H-13), 3.62 (bm, 2H, H-14′), 4.58 (bt, J = 4.8 Hz, 2H, H-12), 6.27 (d, J = 1.2 Hz, 1H, H-3), 7.21 (d, J = 9.0 Hz, 1H, H-6), 7.88 (d, J = 9.0 Hz, 1H, H-5); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 18.90 (C-9), 22.57 (C-16), 24.46 (C-15, 15′), 32.91 (C-11), 55.50 (C-14,14′), 57.16 (C-13), 65.37 (C-12), 110.76 (C-6), 113.61 (C-3), 116.31 (C-4a), 120.69 (C-8), 129.05 (C-5), 152.18 (C-8a), 155.23 (C-4), 157.90 (C-7), 161.80 (C-2), 201.82 (C-10).

*4.4. General procedure for the preparation methiodides of coumarin derivatives **2am**, **3am**, **3bm**, **4am**, **4bm***

Compound **2a**, **3a**, **3b**, **4a** or **4b** (0.5 mmol) was dissolved in diethyl ether then methyl iodide (16 mmol, 1mL) was added. The tightly closed and protected against light flask was stored in the refrigerator for several days. The precipitate was filtered out and dried. The analytical samples were crystallized from absolute ethanol.

*4.4.1. 7-[2-(N-benzyl-N,N-dimethylamino)ethoxy]chromen-2-one iodide (**2am**)*

Yield 68%; m.p.: 161–162 (dec.) °C; IR (KBr) cm^{-1}: 3033 ($\nu_{C-Harom}$), 2963 ($\nu_{C-Hasym}$), 2885 (ν_{C-Hsym}), 1718, 1701 ($\nu_{C=O}$), 1631, 1610 1508, 1455 ($\nu_{C=C}$), 1469 ($\delta_{C-Hasym}$), 1384 (δ_{C-Hsym}), 1285 ($\nu_{C-O-Casym}$), 1054 ($\nu_{C-O-Csym}$), 839 (γ_{C-H}); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 3.09 (s, 6H, H-14, 20), 3.82 (t, J = 4.5 Hz, 2H, H-13), 4.68 (s, 2H, H-15), 4.68 (t, J = 4.5 Hz, 2H, H-12), 6.34 (d, J = 9.6 Hz, 1H, H-3), 7.03 (dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz, 1H, H-6), 7.14 (d, J = 2.4 Hz, 1H, H-8), 7.54–7.62 (m, 5 H, H-17, 17′, 18, 18′, 19), 7.70 (d, J = 8.7 Hz, 1H, H-5), 8.03 (d, J = 9.6 Hz, 1H, H-4); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 49.77 (C-14, 20), 62.07 (C-15), 62.26 (C-13), 67.30 (C-12), 101.68 (C-8), 112.87 (C-6), 112.92 (C-3), 112.98 (C-4a), 127.87 (C-19), 128.95 (C-17, 17′), 129.55 (C-16), 130.37 (C-5), 133.11 (C-18, 18′), 144.23 (C-4), 155.22 (C-8a), 160.12 (C-2), 160.39 (C-7).

*4.4.2. 7-[2-(N,N-Diethyl-N-methylamino)ethoxy]chromen-2-one iodide (**3am**)*

Yield 73%; m.p.: 231.5–232 (dec.) °C; IR (KBr) cm^{-1}: 3055, 3025 ($\nu_{C-Harom}$), 2979, 2952 ($\nu_{C-Hasym}$), 2848 (ν_{C-Hsym}), 1724 ($\nu_{C=O}$), 1612, 1507 ($\nu_{C=C}$), 1450 broad ($\nu_{C=C}$) ($\delta_{C-Hasym}$), 1380 (δ_{C-Hsym}), 1279 ($\nu_{C-O-Casym}$), 1023 ($\nu_{C-O-Csym}$), 837 (γ_{C-H}); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.27 (t, J = 5.7 Hz, 6H, H-15, 15′), 3.06 (s, 3H, H-16), 3.43 (q, J = 5.7 Hz, 4H, H-14, 14′), 3.76 (t, 2H, H-13), 4.55 (t, 2H, H-12), 6.33 (d, J = 9.0 Hz, 1H, H-3), 7.01 (dd, J_1 = 7.5 Hz, 1H, H-6), 7.10 (d, 1H, H-8), 7.69 (d, J = 7.5 Hz, 1H, H-5), 8.02 (d, J = 9.0 Hz, 1H, H-4); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 7.64 (C-15, 15′), 47.27 (C-16), 56.47 (C-14, 14′), 58.40 (C-13), 61.89 (C-12), 101.62 (C-8), 112.81 (C-46), 112.89 (C-3), 112.93 (C-4a), 129.54 (C-5), 144.21 (C-4), 155.19 (C-8a), 160.11 (C-2), 160.35 (C-7).

*4.4.3. 7-[2-(N,N-Diethyl-N-methylamino)ethoxy]4-methylchromen-2-one iodide (**3bm**)*

Yield 79%; m.p.: 206.5–207.5 (dec.) °C; IR (KBr) cm^{-1}: 3033 ($\nu_{C-Harom}$), 2978, 2937 ($\nu_{C-Hasym}$), 2878 (ν_{C-Hsym}), 1702 broad ($\nu_{C=O}$), 1626, 1612, 1510, 1448 ($\nu_{C=C}$), 1461 ($\delta_{C-Hasym}$), 1389 (δ_{C-Hsym}), 1281 ($\nu_{C-O-Casym}$), 1054 ($\nu_{C-O-Csym}$), 843 (γ_{C-H}); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.30 (t, J = 7.2 Hz, 6H, H-15, 15′), 2.42 (s, 3H, H-9), 3.05 (s, 3H, H-16), 3.43 (q, J = 7.2 Hz, 4H, H-14, 14′), 3.76 (bt, J = 6.0 Hz, 2H, H-13), 4.55 (bt, J = 6.0 Hz, 2H, H-12), 6.26 (bq, 1H, H-3), 7.02 (dd, J_1 = 2.4 Hz, J_2 = 8.7 Hz, 1H, H-6), 7.10 (d, J = 2.4 Hz, 1H, H-8), 7.74 (d, J = 8.7 Hz, 1H, H-5); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 7.62 (C-15, 15′), 18.13 (C-9), 47.25 (C-16), 56.44 (C-14, 14′), 58.43 (C-13), 61.85 (C-12), 101.63 (C-8), 111.54 (C-3), 112.54 (C-6), 113.71 (C-4a), 126.56 (C-5), 153.34 (C-4), 154.58 (C-8a), 159.98 (C-2), 160.28 (C-7).

*4.4.4. 7-[2-(1,2-Dimethylpiperidinyl)ethoxy]chromen-2-one iodide (**4am**)*

Yield 27%; m.p.: 207.5–208 (dec.) °C; IR (KBr) cm^{-1}: 3050, 3023 ($\nu_{C-Harom}$), 2941 ($\nu_{C-Hasym}$), 2863 (ν_{C-Hsym}), 1724 ($\nu_{C=O}$), 1610, 1507 ($\nu_{C=C}$), 1461 ($\delta_{C-Hasym}$), 1376 (δ_{C-Hsym}), 1278 ($\nu_{C-O-Casym}$), 1034 ($\nu_{C-O-Csym}$), 844 (γ_{C-H}); Diastereoisomers: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.31, 1.35 (2d, J = 6.6 Hz, 3H, H-19), 1.47–1.93 (m, 6H, H-15, 16, 17), 3.02, 3.20 (s, 3H, H-20), 3.44–3.72 (m, 3H, H-14, H-18), 3.89 (bt, 2H, H-13), 4.52-4.67 (bm, 2H, H-12), 6.34 (d, J = 9.5 Hz, 1H, H-3), 7.02 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1H, H-6), 7.11 (d, J = 2.0 Hz, 1H, H-8), 7.70 (d, J = 8.5 Hz, 1H, H-5), 8.04 (d, J = 9.5 Hz, 1H, H-4); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 14.60, 14.95 (C-19), 19.49, 19.79 (C-16), 20.90 (C-17), 26.99, 27.32 (C-15), 41.06, 50.31, 51.09 (C-20), 60.43, 60.80 (C-14), 61.63, 61.70 (C-12), 62.44 (C-13), 65.52 69.94 (C-18), 101.61, 101.64 (C-8), 112.83 (C-6), 112.89 (C-3), 112.94 (C-4a), 129.54 (C-5), 144.20 (C-4), 155.20 (C-8a), 160.12(C-2), 160.37 (C-7).

4.4.5. 7-[2-(1,2-Dimethylpiperidinyl)ethoxy]4-methylchromen-2-one iodide (**4bm**)

Yield 65%; m.p.: 223.5–224.5 (dec.) °C; IR (KBr) cm^{-1}: 3011 ($\nu_{C-Harom}$), 2943 ($\nu_{C-Hasym}$), 2856 (ν_{C-Hsym}), 1707 ($\nu_{C=O}$), 1617, 1508, 1447 ($\nu_{C=C}$), 1462 ($\delta_{C-Hasym}$), 1392 (δ_{C-Hsym}), 1291 ($\nu_{C-O-Casym}$), 1074 ($\nu_{C-O-Csym}$), 832 (γ_{C-H}); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.33 (2d, $J = 6.5$ Hz, 3H, H-19), 1.51–1.93 (m, 6H, H-15, 16, 17), 2.42 (bs, 3H, H-9), 3.02, 3.20 (2 s, 3H, H-20), 3.44–3.99 (m, 5H, H-13, H-14, H-18), 4.50–4.67 (bm, 2H, H-12), 6.26 (bq, 1H, H-3), 7.02 (bd, $J = 9.0$ Hz, 1H, H-6), 7.10 (bs, 1H, H-8), 7.74 (d, $J = 9.0$ Hz, 1H, H-5); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 14.60, 14.95 (C-19), 18.13 (C-9), 19.50, 19.80 (C-17), 20.91, 20.96 (C-16), 27.00, 27.33 (C-15), 41.05, 50.33, 51.07 (C-20), 60.44, 60.82 (C-13), 61.61, 61.68 (C-12), 62.16 (C-14) 65.54, 69.95 (C-18), 101.61, 101.65 (C-8), 111.52 (C-3), 112.52, 112.56 (C-6), 113.67, 113.71 (C-4a), 126.55 (C-5), 153.33 (C-4), 154.57 (C-8a), 159.97 (C-2), 160.28(C-7).

4.5. X-ray diffraction measurements' details

Crystals of 8-acetyl-7-[2-(1-morpholino)ethoxy]4-methylchromen-2-one (**5d**) suitable for X-ray analysis were grown by slow evaporation from diethyl ether solution. All details of the measurements, crystal data and structure refinement are given in Table 3. The data were collected on an Oxford Diffraction KM4CCD diffractometer [20] at 293 K, using graphite-monochromated MoK_α radiation. The unit cell parameters were determined by least-squares treatment of setting angles of highest-intensity reflections chosen from the whole experiment. Intensity data were corrected for the Lorentz and polarization effects [21]. The structure was solved by direct methods by use the SHELXS97 program [22] and refined by the full-matrix least-squares method with the SHELXL97 program [23]. The function $\Sigma w(|F_o|^2 - |F_c|^2)^2$ was minimized with $w^{-1} = [\sigma^2(F_o)^2 + (0.0655P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$. All non-hydrogen atoms were refined anisotropically. The coordinates of the hydrogen atoms were calculated in idealized positions and refined as a riding model with their thermal parameters calculated as 1.2 (1.5 for methyl group) times U_{eq} of the respective carrier carbon atom. The deposition number CCDC 816034 for **5d** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Table 3
Crystal data, data collection and structure refinement for compound **5d**.

Compound	**5d**
Empirical formula	$C_{18}H_{21}NO_5$
Formula weight	331.36
T (K)	293(2)
Wavelength (Å)	0.71073
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	
a (Å)	7.6038(4)
b (Å)	21.734(1)
c (Å)	10.3668(5)
β (°)	103.408(5)
Volume (Å^3)	1666.5(1)
Z, D_x (mg/m^3)	4, 1.321
μ (mm^{-1})	0.097
F(000)	704
θ range for data collection (°)	4.12–26.02
hkl range	$-9 \le h \le 9$ $-19 \le k \le 26$ $-12 \le l \le 9$
Reflections	
Collected	5915
Unique (R_{int})	3183(0.012)
Observed ($I > 2\sigma(I)$)	2193
Data/restraints/parameters	3183/0/217
Absorption correction	Multi-scan
Goodness-of-fit on F^2	1.07
$R(F)$ ($I > 2\sigma(I)$)	0.0393
$wR(F^2)$ (all data)	0.1140
Max/min. $\Delta\rho$ (e/Å^3)	0.274/−0.210

4.6. Antibacterial evaluation

The following microbial strains with various cell wall structures were chosen: bacteria Gram-positive: *S. aureus* ATCC 6538, *S. aureus* ATCC 6538P, *M. luteus* ATCC 9341, *M. luteus* ATCC 10240, *B. subtilis* ATCC 6633, *B. cereus* ATCC 11778, bacteria Gram-negative: *Escherichia coli* ATCC 8739, *E. coli* ATCC 10536, *Pseudomonas aeruginosa* ATCC 27853, *P. aeruginosa* ATCC 15442 and fungi (yeast strains): *Candida albicans* ATCC 10231, *Candida parapsilosis* ATCC 22019. The cylinder-plate method was used in the preliminary antimicrobial activity tests [24]. The 100 μL of compound was placed into the cylinder in suspension of 10% DMSO in a 0.08 M phosphate buffer with pH 7.0. The cylinders were put on a Muller–Hinton 2 or Sabouraud agar plate inoculated with one of the tested strains. The plates with bacterial strains were incubated at 37 °C for 24 h and plates with yeast strains at 30 °C for 48 h. Minimal inhibitory concentration (MIC) was obtained by mixed with 19 mL of a Mueller–Hinton 2 Agar, cooled to 56 °C with 1 mL of appropriate dilution of the tested compound. Then 2 μL of a particular cell suspension of optical density 0.5 unit on the McFarland scale was applied to the surface of the agar. The lowest concentration of tested compound which totally inhibited growth of examined strain was evaluated as MIC value [25]. In control samples, MIC values of ciprofloxacin ranging between 0.08 and 1.36×10^{-3} μmol/mL for bacterial strains.

Appendix. Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.ejmech.2011.03.006.

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